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

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

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ABSTRACT [300 words]

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

DESIGN
Parallel, double-blinded, randomised controlled trial.

SETTING
Emergency department attendances and general practice referrals within twenty hospitals in England.

INTERVENTIONS
Flucloxacillin, at a minimum dose and duration 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
The 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. There was no significant difference in the number of patients stating that they had returned to normal activities at the Day 30 interview in the flucloxacillin with clindamycin allocation (99/121, 82%) versus flucloxacillin alone (104/129, 81%) – adjusted OR 0.90 (95% CI 0.44 to 1.84).

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 diarrhoea within the first few days.

TRIAL REGISTRATION
ClinicalTrials.gov Identifier: NCT01876628
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.
INTRODUCTION

Cellulitis is a common acute skin infection occurring anywhere on the body, which causes pain, swelling and erythema. It cannot be reliably distinguished from erysipelas which may be considered a form of cellulitis.[1] Cellulitis may be accompanied by fever and other systemic features. A UK study in 1992[2] estimated a cellulitis incidence rate of 16.4 per 1000 person-years in patients presenting to general practice. In England alone during 2012, people admitted with a diagnosis of cellulitis took up 400,000 bed days.[3]

Microbiological studies are positive in only a quarter of people who present to hospital with erysipelas or cellulitis. The use of latex agglutination techniques and direct immunofluorescence on skin biopsy specimens increases the yield and has shown that beta haemolytic streptococci, usually group A streptococci (GAS) or group G, represent the most prominent bacteria in studies of cellulitis and erysipelas, accounting for almost 80% of isolated organisms.[4,5] Molecular testing[6] and serology[7] have been found to be of variable value but can improve the yield especially if the patient has received antibiotics.[8] It is probable that Staphylococcus aureus is not the causative agent in most cases where it was isolated, adopting an opportunistic bystander role. This is supported by a study which demonstrated no extra benefit when adding an antibiotic active against meticillin resistant S.aureus (MRSA) in the presence of MRSA carriage.[9]

Standard therapy is with a beta-lactam antibiotic; commonly flucloxacillin or a cefalosporin, which whilst effective,[10] often leaves the patient with significant skin damage which takes many weeks to heal. Beta-lactams need a growing or dividing bacterium in order to work. Clindamycin, a protein inhibiting antibiotic, inhibits toxin production and is able to kill intracellular streptococci.[11, 12] It is these toxins which are responsible for local damage and systemic features.[13] Protein inhibiting antibiotics are part of recommended therapy for invasive GAS infections such as necrotising fasciitis and pleural empyema but there is conflicting evidence of any benefit[14, 15] and there are no clinical trials to support it. The evidence for an effect in reducing toxin has been predominantly in-vitro and even in-vitro studies show antagonism under some conditions,[16] but one retrospective and one prospective review showed benefit of clindamycin, in invasive infections caused by GAS.[17, 18].

Clindamycin is a recommended treatment for cellulitis in the British National Formulary;[19] it is a lincosamide and is also active against some macrolide (e.g. clarithromycin) resistant strains of streptococci and staphylococci. It was the second most common treatment for cellulitis in a survey of Canadian hospitals[20] and clindamycin or clarithromycin featured in every one of 23 guidelines examined as part of a review of treatment of cellulitis in the south west of England.[21] If clindamycin is an effective adjuvant in serious streptococcal infections, its benefit should be detectable in cellulitis. A reduction in toxin production should lead to a reduction in the severity of infection and result in less pain, more rapid resolution, improved short-term health-related quality of life, and a more rapid return to normal activity.

This trial was designed to determine whether clindamycin has an additional beneficial effect in cellulitis. Clear evidence that clindamycin has no benefit would have implications for the use of it as adjunctive or sequential therapy in cellulitis. Failure to demonstrate benefit would also suggest that the present recommendations for its use in invasive GAS infections need to be re-evaluated.
METHODS

Trial design and participants

We conducted a double-blind, randomised, placebo-controlled trial from October 2013 to December 2015, with 1:1 parallel group allocation. Potential participants were screened from emergency departments, hospital inpatients and referrals to hospital from general practice (family physicians) from 20 hospitals in England.

The diagnosis of cellulitis was supported using a set of criteria established for the PATCH trials on the prevention of recurrent cellulitis.[22] All adult patients with unilateral limb cellulitis were eligible; the key exclusion criteria were antibiotic treatment for longer than 48 hours, previous Clostridium difficile infection, past MRSA carriage, allergy to either penicillin or clindamycin and pre-existing diarrhoea. We collected data on randomised and non-randomised participants as specified by CONSORT (Figure).

All participants were given flucloxacillin orally or intravenously, the dose and route was decided by the clinical team treating the patient. The minimum dose and duration of flucloxacillin specified in the protocol was 500mg four times per day orally for five days. Participants on other beta-lactams prior to recruitment, e.g. co-amoxiclav, were switched to flucloxacillin.

The dose of clindamycin in this trial was 300mg four times per day orally, which has been used in a large trial of skin and soft tissue infections,[23] and the duration was two days. The duration was designed to achieve adequate tissue levels of clindamycin whilst minimising the side effects. The protocol specified that clindamycin or placebo was to be started within 48 hours of starting the beta-lactam. This period was a compromise between giving the patient adequate time to consider the trial and minimise the duration of any preceding beta-lactam antibiotic, which might reduce any effect of clindamycin.

Randomisation and masking

Randomisation was web-based with blocks of 8 and stratified by age (<65 and >64) and part of the week to allow for variation in follow-up caused by weekends. The randomisation system provided a study number and study drug bottle number. Study medication was prepared and dispensed by the University Hospitals Bristol Pharmacy which provided batches of the medication bottles to the study sites. Both clindamycin and placebo were formulated and supplied in identical capsules sealed in identical medication bottles. Only the pharmacy kept the code of whether the bottle contained clindamycin or placebo. The pharmacy had no access to the clinical data or patient identification unless unblinding was required. The study nurses, the statistician, and all investigators and participants were blind to whether the bottle contained clindamycin or placebo.

Procedures

The study schedule consisted of three face-to-face visits, at Baseline, Day 5 and Day 10, with a telephone follow-up at Day 30. At the first three visits we measured standard observations (core temperature, pulse, blood pressure and respiration rate). We also took blood for a full blood count, renal function, C-reactive protein and albumin. We estimated the affected skin area of the limb using a scoring system similar to that used in psoriasis[24] from which we calculated the percentage of...
body skin area. We measured the limb circumference at its greatest over the affected area and the
highest temperature from the affected area and took comparable measurements from the
unaffected limb, if available. The temperature measurements were made with an infra-red
thermometer,[25] limb circumference with a disposable tape-measure and pain scores were
measured using a visual analogue scale (VAS). A record of adverse events was made at each visit.
The actual number of days after randomisation on which follow-up occurred was variable. The day of
follow-up was dependent on the patients’ circumstances and, rather than lose a patient to follow-
up, we asked patients to attend whenever they could, whilst still maintaining the target of four days
post randomisation. We asked patients to return the study drug containers and counted remaining
capsules.

We collected additional information, including Euroqol (EQ-5D-5L) and Health Today scores, at
Baseline and Day 30 for a health economics analysis. We asked patients at each visit and at the Day
30 telephone follow-up whether or not they considered themselves to be back to their normal
activities. At Baseline we recorded the time between the onset of systemic features, if reported, and
local features. We recorded the time that antibiotics were first taken. We asked the patients about
previous surgery, trauma or cellulitis of the affected limb and whether they had been diagnosed as
having lymphoedema or diabetes mellitus as these are recognised risk factors.[26]

Outcomes

The primary outcome was improvement at the Day 5 follow-up visit, defined as being afebrile
(<37.5°C) and having a reduction in limb swelling (measured by limb circumference) or a reduction in
erythema (measured by skin-surface temperature) of 0.2 standard deviations or more. The reduction
in limb swelling and limb temperature used the difference between affected and unaffected limbs to
reduce confounding by ambient temperature, clothing and posture. These three clinical features
were chosen because they could be measured accurately. 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.

Statistics

The estimated number improving in the placebo group at first follow-up was 80%. A two group
continuity corrected chi-squared test with a 0.05 two-sided significance level will have 80% power to
detect the difference between 80% improving in the placebo group and 90% improving in the
clindamycin group (odds ratio of 2.250 ) when the sample size with complete data in each group is
219 (total 438). There was no interim analysis and there were no pre-specified sub-group analyses.
The trial was stopped at 26 months, with 410 patients randomised, for funding reasons.

Data was analysed on an intention to treat basis. A Fishers exact test, with odds ratios (OR), was
used to determine whether there was a difference in those improving in each group at first follow-
up (Day 5). The analysis of the secondary outcomes adjusted for some baseline imbalances between
the treatment allocations (namely baseline total affected area, difference between baseline affected
and unaffected limb temperature, difference between baseline affected and unaffected limb
circumferences and the logarithm of neutrophil count). The analysis of the primary outcome was
also repeated adjusting for these factors. Continuous outcomes were analysed using analysis of
covariance (ANCOVA) and also adjusted for the baseline value of the outcome as well as the baseline imbalances. For dichotomous outcomes, logistic regression analysis was used to compare the adjusted odds of the outcome by treatment group. For continuous outcomes, there were some occasions where the distribution of the data was such that the logarithm of the outcome was used in the ANCOVA and there were also a few occasions when the assumptions for the ANCOVA were not met so it was necessary to use a Mann-Whitney test to compare the allocations. Medians have been reported instead of means where the data is markedly skewed.

**PATIENT INVOLVEMENT**

Patients were not involved in designing the study apart from the patient information sheet. We used qualitative study data collected previously, which highlighted patient comfort as important, to inform the choice of outcomes.[27, 28] The Day 30 telephone consultation asked for feedback and comments on the conduct of the study. Towards the end of the study we arranged a meeting and an on-line survey focusing on patients’ symptoms and non-pharmacological interventions.

**RESULTS**

**Baseline**

2444 patients with a diagnosis of cellulitis were screened for eligibility. 410 patients were randomised, ranging from 18 to 95 years. Nine patients were subsequently found to be ineligible because they had received more than 48 hours of antibiotics (5 patients) or the diagnosis was incorrect (4 patients). The flow chart (Figure) summarises the numbers of patients screened for eligibility and numbers present at each follow-up. All patients randomised are included in the intention to treat (ITT) population. The baseline characteristics of the randomised patients is summarised in Table 1; not every patient had a complete set of baseline data. The clindamycin allocation patients were slightly younger and had less severe cellulitis. Overall 55 (13%) patients had a history of previous surgery, 63 (15%) of trauma to and 132 (32%) of cellulitis of the affected limb. Nineteen (5%) had a diagnosis of lymphoedema and 36 (9%) of diabetes mellitus.

**Withdrawal from the study and non-attendance at Day 5**

Six patients were found to be ineligible immediately after randomisation and did not receive the study drug (5 clindamycin and 1 placebo). The most common reason for active withdrawal from the study was that the patient was given open label clindamycin either unintentionally (4 patients) or intentionally (12 patients).

Four patients given open label clindamycin before Day 5 are included in the analysis of primary outcome; two in the clindamycin allocation and two in the placebo allocation.

Withdrawals also occurred because the patient no longer wished to continue for personal reasons (9 patients) or because of adverse events (3 patients). Some patients did not attend and gave no reason. We looked at the baseline characteristics of those patients who did not attend the Day 5 follow-up and compared them with those that did. We found that the non-attendees, as a group, were significantly younger, were significantly less likely to have leg cellulitis, had a smaller affected skin area but with slightly higher neutrophil counts. There were no differences in the baseline characteristics of the non-attendees between the study drug allocations.
Primary outcome and Day 5 follow-up

We were able to calculate the primary outcome for 328 patients. Those with missing data on temperature at Day 5, or the three with missing unaffected limb data, were categorised as having missing data for primary outcome. Patients with temperature data, but with missing data on both limb circumference and limb temperature, were categorised as not improved, rather than missing. Patients with temperature data, and with either a measure for change in circumference or change in limb temperature, were categorised according to the two out of three data items they had available.

The median number of days to follow-up was 4.0 for clindamycin and 4.1 for placebo.

Within the evaluable population there was no significant difference in improvement which was 87.2% for clindamycin and 81.4% for placebo; OR 1.55 (95% CI 0.81 to 3.01), p=0.174 (Table 2). Adjusting for baseline differences did not alter the primary outcome result. As a proportion of those patients randomised improvement occurred in 67.0% of those on clindamycin compared to 67.6% those on placebo; OR 0.97 (95% CI 0.63 to 1.50), p=0.916.

Sub-group analyses

We did not specify any sub-group analysis in the study protocol but in order to clarify whether there might have been a positive effect from clindamycin in a sub-population and a negative, or neutral effect, in another sub-population we undertook sub-group analyses. We looked at severity as defined as having a systemic inflammatory response syndrome (SIRS) score of zero or more than zero; duration of local features (area, skin temperature and swelling) of between 48 and 84 hours, or less than 48 hours prior to randomisation; duration of antibiotics prior to the study drug of greater or less than 12 hours. No statistically significant difference in improvement in any sub-group was found.

Compliance

The majority of the study drugs were taken; 148/159 (93%) in the clindamycin group and 159/176 (90%) of the placebo group had zero capsules remaining. The mean number of capsules remaining of the 11/159 in the clindamycin allocation was 6.5 and of the 17/176 in the placebo allocation was 4.4.

Day 10 follow-up and secondary outcomes

Fifty-four patients who attended at Day 5 did not attend at Day 10. The non-attendees were younger but otherwise similar to those that attended Day 5. There was no significant difference in any secondary outcome measures except a slightly lower mean blood pressure (systolic , 3 mm Hg) in the clindamycin allocation at Day 10 and lower median lymphocyte counts in the clindamycin allocation at both Day 5 and Day 10 (0.18 and 0.19 X 10^9/L respectively). The median number of days to follow-up was 9 days in both allocations. Table 3 summarises the secondary outcomes at Day 5 and at Day 10.

Back to normal activities

At Day 5 76/158 (48%) of the clindamycin allocation were back to normal activities compared to 74/175 (42%) of the placebo allocation (OR 1.09 (CI 0.66 to 1.78), p=0.739). At Day 10 77/133 (58%)
of the clindamycin allocation were back to normal activities compared to 82/153 (54%) of the placebo allocation (OR 1.13 (CI 0.67 to 1.89), p=0.646). At the Day 30 follow up the median duration from recruitment was 38.4 days in both allocations. Two hundred and fifty patients had a response to the question on their return to normal activities; 99/121 (82%) in the clindamycin allocation were back to normal activities compared to 104/129 (81%) in the placebo allocation (OR 0.90 (95% CI 0.44 to 1.84), p=0.774). The odds ratios are adjusted odds ratios adjusting for total affected area, difference in limb circumference, difference in limb temperature and neutrophil at baseline.

Adverse events

Diarrhoea was the most common adverse event in the clindamycin allocation with 34/158 (22%) of the clindamycin allocation reporting it compared to 16/172 (9%) in the placebo allocation (OR 2.7 (95% CI 1.41 to 5.07), p=0.002) (Table 4). Adverse events resulted in three patients leaving the trial before Day 5. Any hospital admission, for any reason, after recruitment and during the first 10 days of follow-up was recorded as a serious adverse event (SAE). There were 23 SAE (8 in the clindamycin allocation and 15 in the placebo allocation) and none were thought to be related to their study drug treatment. No case of *Clostridium difficile* infection was reported. Two patients died before Day 30 and of causes unrelated to cellulitis or their treatment (one myocardial infarction and one pulmonary embolus) both were in the placebo allocation.

DISCUSSION

The results of this clinical trial do not provide evidence that any feature of cellulitis was improved by the addition of clindamycin. We collected a wide array of objective data in order to detect particular effects of clindamycin which might be related to toxin production and none showed any effect. The range of severity in the study patients was wide; we included those both on oral and intravenous flucloxacillin therapy. We looked to see whether clindamycin’s effects may be only evident in those with more severe disease, in those who had a shorter duration of features or those who had antibiotic treatment earlier. We could find no evidence that any of these circumstances made the addition of clindamycin beneficial. However, we did find that the proportion of patients in the clindamycin allocation with diarrhoea, up to Day 5, was double that of the patients receiving placebo.

This study has some weaknesses; about 20% of patients did not attend the first follow up but this is a feature of an acute infection which, in many people heals rapidly, and of the population attending emergency departments. We were unable to find any significant differences in attendance between the two study allocations that could not be accounted for by the marginal differences in severity. We were unsure of what duration we should allow between initial antibiotic therapy and clindamycin but we could find no significant difference in outcome when we compared those having started antibiotics within 12 hours with those between 12 and 48 hours. We were also uncertain about the appropriate duration of clindamycin to detect an effect if it was present. We did detect an effect, an adverse one; diarrhoea, with the 48 hour duration.

This study was developed as a result of a south west England regional review of treatment of proven group A streptococcal (GAS) infection which was undertaken in 2011. As part of this review we could find no evidence of benefit of the addition of clindamycin despite its widespread and increasing use. This led us to look at a way of testing the hypothesis that clindamycin’s protein-inhibiting activity is
of benefit in GAS infection. There had been no previous studies on adjunctive clindamycin in cellulitis and we thought this study would be helpful both in the management of cellulitis and invasive GAS infections. This study was designed to test the hypothesis that a toxin-inhibiting antibiotic, of which clindamycin is the exemplar, is effective in streptococcal infections. Cellulitis is a common streptococcal infection with easy-to-measure objective features and has been used in this trial as a representative streptococcal infection. We think it is reasonable to generalise the results of this trial to other streptococcal infections in the absence of specific trials.

The in-vitro evidence that supported clindamycin’s benefits is conflicting and the clinical evidence of benefit in invasive GAS infections has the biases intrinsic in these retrospective and prospective studies:[17, 18] patient selection, patient treatment, recall and publication. The principal reason for the unsupported use of clindamycin in cellulitis is a widespread misunderstanding of the natural history of the condition. The local features of cellulitis will often progress (or at least not improve) for several days after presentation. An increasing affected area with mild fever and rising CRP leads both patient and physician to believe that the antibiotic treatment is failing; this is despite the patient’s systemic symptoms of rigors, nausea and anorexia improving. The addition of clindamycin or change to intravenous therapy is consequently and spuriously attributed as being responsible for the patient’s improvement. The fact that 16 patients were intentionally given clindamycin and withdrawn from the trial is a reflection of the belief in clindamycin’s powers. It is probable that by the time the patient presents to a healthcare professional with local signs of cellulitis the various toxins have bound to their targets and initiated the exaggerated inflammatory response which is part of the cause of skin damage. At this point the streptococcus is replicating and susceptible to beta-lactam antibiotics, or no longer viable, so the addition of another antibiotic will have no beneficial effect. The mechanisms are similar to those of envenoming[29] and it is unsurprising that drugs thought to reduce toxin production given days later are unlikely to be effective.

The Cochrane review of interventions in cellulitis found no difference in outcome, however measured, between treatment with a beta-lactam versus either macrolides or streptogramin.[10] A large trial comparing dicloxacillin with clindamycin in the treatment of skin infections found no difference in efficacy.[23] These studies support the outcome of this trial; because if toxin inhibition was of importance then the superiority of clindamycin should have been evident.

This clinical trial has shown that adjunctive clindamycin has no effect on improving outcome in cellulitis. Its only real effect is increasing the likelihood of diarrhoea with a rate comparable to that previously recorded.[23, 30] It also is likely that there is no benefit in invasive GAS disease. Any further use of adjunctive clindamycin and other protein-inhibiting antibiotics, either concurrently or sequentially, for the treatment of streptococcal and staphylococcal infections should only be within a clinical trial.
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Kim Thomas and Katharine Foster, Centre of Evidence Based Dermatology; trial design and documentation

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Trial steering committee

The trial steering committee was chaired by Richard Gray with Tristan Clark and Richard Thomson.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: the study was funded by the UK National Institute for Health Research’s (NIHR) Research for Patient Benefit (RfPB) programme; no financial relationship with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

CONTRIBUTORS

RB conceived the concept, designed and supervised the study. RB and OMW analysed and interpreted the data. RB and PF drafted the manuscript. PD, TH and HJ all contributed to data collection. ADH contributed to the design and methodology. All authors were involved in data interpretation, contributed to, and approval of, the final manuscript.

RB is the guarantor
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ETHICAL APPROVAL

The trial was approved by the UK National Research Ethics Service (reference number: 13/SC/0211) and informed consent was obtained from all participants.

TRANSPARENCY

The authors affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

DATA SHARING AND TRIAL PROTOCOL

Anonymised patient level data are available on reasonable request from the corresponding author. The full trial protocol is available from the corresponding author.

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DOI: 10.1002/9780470015902.a0002188.pub3

**Figure.** C4C CONSORT diagram

Assessed for eligibility based on diagnosis 2444

Excluded 2034

Reasons for exclusion:
- >48 hours beta-lactam 535
- Penicillin allergy 225
- Participation declined 148
- Not limb cellulitis 138
- Geographical 131
- Clindamycin recently 106
- Other reasons 329
- No reasons given 422

Randomisation stratified by:
- Age: less or greater than 65
- Part of week recruited:
  - Monday to Wednesday
  - Thursday to Sunday

Randomised and Intention to Treat population 410

Clindamycin 203
- Found to be ineligible 6
- Given open-label clindamycin 7

Placebo 207
- Found to be ineligible 3
- Given open-label clindamycin 9

Clindamycin

Day 5 follow-up
- 336 (82%)

Sufficient data at Day 5 for determining Primary Outcome 328 (80%)

Placebo

Day 5 follow-up
- 31 (82%)

Sufficient data at Day 5 for determining Primary Outcome 27 (80%)

Did not attend Day 5
- 43
- 31

Evaluable at Day 5
- 160
- 176

Adverse events
- 46
- 27

Did not attend Day 10
- 68
- 56

Evaluable at Day 10
- 135
- 151

Adverse events
- 19
- 19

Uncontactable Day 30
- 80
- 77

Evaluable at Day 30
- 123
- 130

Deaths before Day 30
- 0
- 2
Table 1. Baseline characteristics of the randomised patients. Figures are numbers of patients (percentage) unless otherwise stated.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clindamycin (n=203)</th>
<th>Placebo (n=207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age in years</td>
<td>47.7 (18.4)</td>
<td>50.5 (16.9)</td>
</tr>
<tr>
<td>Male</td>
<td>129 (64)</td>
<td>149 (72)</td>
</tr>
<tr>
<td>Leg affected</td>
<td>150 (74)</td>
<td>149 (72)</td>
</tr>
<tr>
<td>Duration of local features before starting study drug (days); Median (IQR)</td>
<td>2.1 (2.1)</td>
<td>2.0 (2.1)</td>
</tr>
<tr>
<td>Duration of preceding antibiotics before starting study drug (hours); Median (IQR)</td>
<td>1.9 (19.0)</td>
<td>6.5 (23.5)</td>
</tr>
<tr>
<td>Temperature (°C); Mean (SD)</td>
<td>36.8 (0.5)</td>
<td>36.9 (0.7)</td>
</tr>
<tr>
<td>Pulse (beats per minute); Mean (SD)</td>
<td>81 (15)</td>
<td>81 (14)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg); Mean (SD)</td>
<td>131 (20)</td>
<td>128 (18)</td>
</tr>
<tr>
<td>Affected skin area as percentage of body surface area; Median and IQR</td>
<td>4 (4)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Difference in circumference between affected and unaffected limb (cm); Mean (SD)</td>
<td>2.5 (2.1)</td>
<td>2.9 (2.1)</td>
</tr>
<tr>
<td>Difference in surface temperature between affected and unaffected limb (°C); Mean (SD)</td>
<td>2.5 (1.9)</td>
<td>2.7 (1.6)</td>
</tr>
<tr>
<td>Neutrophil (X 10^9/L); Median (IQR)</td>
<td>6.3 (4.6)</td>
<td>7.0 (4.9)</td>
</tr>
<tr>
<td>Lymphocyte (X 10^9/L); Median (IQR)</td>
<td>1.6 (0.7)</td>
<td>1.5 (1.1)</td>
</tr>
<tr>
<td>Urea (mmol/L); Median (IQR)</td>
<td>5.0 (2.1)</td>
<td>4.9 (2.1)</td>
</tr>
<tr>
<td>Albumin (g/L); Median (IQR)</td>
<td>39 (7)</td>
<td>38 (8)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L); Median (IQR)</td>
<td>23 (80)</td>
<td>54 (119)</td>
</tr>
<tr>
<td>Pain score (VAS); Median (IQR)</td>
<td>5 (4)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>SIRS score ≥1*</td>
<td>83/200 (42)</td>
<td>96/207 (46)</td>
</tr>
</tbody>
</table>

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 (WBC count derived from neutrophils plus lymphocytes plus 1)
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)

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

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)

<table>
<thead>
<tr>
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<th>Time point</th>
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<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C); Mean</td>
<td>Baseline</td>
<td>36.8</td>
<td>36.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>36.6</td>
<td>36.5</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>36.5</td>
<td>36.5</td>
<td>0.74</td>
</tr>
<tr>
<td>Pulse (beats per minute); Mean</td>
<td>Baseline</td>
<td>80</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>78</td>
<td>76</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>78</td>
<td>77</td>
<td>0.76</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg); Mean</td>
<td>Baseline</td>
<td>131</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>129</td>
<td>131</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>128</td>
<td>131</td>
<td>0.02</td>
</tr>
<tr>
<td>Affected skin area as percentage of body surface area; Median</td>
<td>Baseline</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>2</td>
<td>2</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>1</td>
<td>1</td>
<td>0.67</td>
</tr>
<tr>
<td>Difference in circumference between affected and unaffected limb (cm); Mean</td>
<td>Baseline</td>
<td>2.67</td>
<td>2.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>2.04</td>
<td>2.18</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>1.42</td>
<td>1.77</td>
<td>0.90</td>
</tr>
<tr>
<td>Difference in surface temperature between affected and unaffected limb (°C); Mean</td>
<td>Baseline</td>
<td>2.49</td>
<td>2.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>1.15</td>
<td>1.57</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>0.87</td>
<td>1.13</td>
<td>0.65</td>
</tr>
<tr>
<td>Neutrophil (X 10^9/L); Median</td>
<td>Baseline</td>
<td>5.97</td>
<td>6.95</td>
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<tr>
<td></td>
<td>Day 5</td>
<td>4.24</td>
<td>4.43</td>
<td>0.95</td>
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<td></td>
<td>Day 10</td>
<td>4.18</td>
<td>4.32</td>
<td>0.86</td>
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<tr>
<td>Lymphocyte (X 10^9/L); Median</td>
<td>Baseline</td>
<td>1.51</td>
<td>1.50</td>
<td></td>
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<tr>
<td></td>
<td>Day 5</td>
<td>1.70</td>
<td>1.88</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>1.75</td>
<td>1.94</td>
<td>0.01</td>
</tr>
<tr>
<td>Urea (mmol/L); Median</td>
<td>Baseline</td>
<td>5.0</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>4.8</td>
<td>5.0</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>4.9</td>
<td>5.2</td>
<td>0.37</td>
</tr>
<tr>
<td>Albumin (g/L); Median</td>
<td>Baseline</td>
<td>38</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>38</td>
<td>37</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>39</td>
<td>38</td>
<td>0.63</td>
</tr>
<tr>
<td>C-reactive protein (mg/L); Median</td>
<td>Baseline</td>
<td>22</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>10</td>
<td>16</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>5</td>
<td>6</td>
<td>0.20</td>
</tr>
<tr>
<td>Pain score (VAS); Median</td>
<td>Baseline</td>
<td>4.5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>2</td>
<td>2</td>
<td>0.30*</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>0</td>
<td>1</td>
<td>0.61</td>
</tr>
</tbody>
</table>

The baseline values are of those patients who attended Day 5. The baseline values for those attending Day 10 are similar to the Day 5 baseline values.

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

<table>
<thead>
<tr>
<th></th>
<th>Clindamycin</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reported at Day 5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>3 (1.9)</td>
<td>8 (4.6)</td>
<td>0.223</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>34 (21.5)</td>
<td>16 (9.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Any adverse event (including rash and diarrhoea)*</td>
<td>46 (28.9)</td>
<td>27 (15.6)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Reported at Day 10</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2 (1.5)</td>
<td>10 (6.7)</td>
<td>0.039</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>17 (12.8)</td>
<td>8 (5.3)</td>
<td>0.035</td>
</tr>
<tr>
<td>Any adverse event (including rash and diarrhoea)*</td>
<td>19 (14.1)</td>
<td>19 (12.6)</td>
<td>0.731</td>
</tr>
</tbody>
</table>

*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.
Assessed for eligibility (n=2444)

Excluded (n=2034) Reasons for exclusion:
- Greater than 48 hours of a beta-lactam (n=535)
- Penicillin allergy (n=225)
- Declined to participate (n=148)
- Not limb cellulitis (n=138)
- Out of area and unable to attend follow-up (n=131)
- Clindamycin within the last 30 days (n=106)
- Other reasons (n=329), No reasons recorded (n=422)

Randomised and intention to treat population 410

Randomised to receive clindamycin (n=203)
- Received clindamycin (n=199)
- Found to be ineligible (n=6)
- Given open-label clindamycin (n=7)

Analysed by intention to treat (n=203)
- Analysed for primary outcome (n=156)
- Insufficient data for primary outcome (n=4)
- Did not attend Day 5 (n=43)

Evaluable at Day 10 (n=135)
- Did not attend Day 10 (n=68)

Evaluable at Day 30 (n=123)
- Uncontactable Day 30 (n=80)

Randomised to receive placebo (n=207)
- Received placebo (n=206)
- Found to be ineligible (n=3)
- Given open-label clindamycin (n=9)

Analysed by intention to treat (n=207)
- Analysed for primary outcome (n=172)
- Insufficient data for primary outcome (n=4)
- Did not attend Day 5 (n=31)

Evaluable at Day 10 (n=151)
- Did not attend Day 10 (n=56)

Evaluable at Day 30 (n=130)
- Uncontactable Day 30 (n=77)
**C4C Trial CONSORT 2010 checklist of information to include** *

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on page No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td>1a</td>
<td>Identification as a randomised trial in the title</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
<td>5</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
<td>6</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td>6</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>7a</td>
<td>How sample size was determined</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Randomisation:</strong></td>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8b</td>
<td>Type of randomisation; details of any restriction (such as blocking and block size)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
<td>6</td>
</tr>
<tr>
<td><strong>Implementation</strong></td>
<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
<td>6</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those</td>
<td>6</td>
</tr>
</tbody>
</table>

*CONSORT 2010 checklist*
<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11b</td>
<td>If relevant, description of the similarity of interventions</td>
</tr>
<tr>
<td>12a</td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
</tr>
<tr>
<td>12b</td>
<td>Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
</tr>
<tr>
<td>13a</td>
<td>For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</td>
</tr>
<tr>
<td>13b</td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
</tr>
<tr>
<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
</tr>
<tr>
<td>14b</td>
<td>Why the trial ended or was stopped</td>
</tr>
<tr>
<td>15</td>
<td>A table showing baseline demographic and clinical characteristics for each group</td>
</tr>
<tr>
<td>16</td>
<td>For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
</tr>
<tr>
<td>17a</td>
<td>For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
</tr>
<tr>
<td>17b</td>
<td>For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
</tr>
<tr>
<td>18</td>
<td>Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory</td>
</tr>
<tr>
<td>19</td>
<td>All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)</td>
</tr>
<tr>
<td>20</td>
<td>Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
</tr>
<tr>
<td>21</td>
<td>Generalisability (external validity, applicability) of the trial findings</td>
</tr>
<tr>
<td>22</td>
<td>Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence</td>
</tr>
<tr>
<td>23</td>
<td>Registration number and name of trial registry</td>
</tr>
<tr>
<td>24</td>
<td>Where the full trial protocol can be accessed, if available</td>
</tr>
<tr>
<td>25</td>
<td>Sources of funding and other support (such as supply of drugs), role of funders</td>
</tr>
</tbody>
</table>

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).*
Adjunctive clindamycin for cellulitis: clinical trial comparing flucloxacillin with or without clindamycin for the treatment of limb cellulitis

<table>
<thead>
<tr>
<th>Journal:</th>
<th>BMJ Open</th>
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<td>Research</td>
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<tr>
<td>Date Submitted by the Author:</td>
<td>23-Nov-2016</td>
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<td>Complete List of Authors:</td>
<td>Brindle, Richard; University Hospitals Bristol, Microbiology and Infectious Diseases Williams, Owen; University Hospitals Bristol, Microbiology and Infectious Diseases Davies, Paul; University Hospitals Bristol, General Practice Support Unit Harris, Tim; Barts Health NHS Trust and Queen Mary University of London, Whitechapel Rd, London E1 1BB, Emergency Medicine Jarman, Heather; St George's University Hospitals, Emergency Care Hay, Alastair; University of Bristol, Academic Unit of Primary Health Care Featherstone, Peter; Portsmouth Hospitals NHS Trust, Acute Medicine Unit</td>
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<td>cellulitis, erysipelas, flucloxacillin, clindamycin, limb, diarrhoea</td>
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Adjunctive clindamycin for cellulitis: clinical trial comparing flucloxacillin with or without clindamycin for the treatment of limb cellulitis

AUTHORS

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Key words: cellulitis, flucloxacillin, clindamycin, limb, diarrhoea

Word count: 3694

Figures: 1
Tables: 4
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ABSTRACT [300 words]

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

DESIGN
Parallel, double-blinded, randomised controlled trial.

SETTING
Emergency department attendances and general practice referrals within twenty hospitals in England.

INTERVENTIONS
Flucloxacillin, at a 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
The 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. There was no significant difference in the number of patients stating that they had returned to normal activities at the Day 30 interview in the flucloxacillin with clindamycin allocation (99/121, 82%) versus flucloxacillin alone (104/129, 81%) – adjusted OR 0.90 (95% CI 0.44 to 1.84).

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 diarrhoea within the first few days.

TRIAL REGISTRATION
ClinicalTrials.gov Identifier: NCT01876628
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.
INTRODUCTION

Cellulitis is a common acute skin infection occurring anywhere on the body, which causes pain, swelling and erythema. It cannot be reliably distinguished from erysipelas which may be considered a form of cellulitis.[1] Cellulitis may be accompanied by fever and other systemic features. A UK study in 1992[2] estimated a cellulitis incidence rate of 16.4 per 1000 person-years in patients presenting to general practice. In England alone during 2012, people admitted with a diagnosis of cellulitis took up 400,000 bed days.[3]

Microbiological studies are positive in a variable proportion of people who present to hospital with erysipelas or cellulitis. The use of latex agglutination techniques and direct immunofluorescence on skin biopsy specimens increases the yield and has shown that beta haemolytic streptococci, usually group A streptococci (GAS) or group G, represent the most prominent bacteria in studies of cellulitis and erysipelas, accounting for almost 80% of isolated organisms.[4,5] Molecular testing[6] and serology[7] have been found to be of variable value but can improve the yield especially if the patient has received antibiotics.[8] It is probable that *Staphylococcus aureus* is not the causative agent in most cases where it was isolated, adopting an opportunistic bystander role. This is supported by a study which demonstrated no extra benefit when adding an antibiotic active against meticillin resistant *S.aureus* (MRSA) in the presence of MRSA carriage.[9]

Standard therapy is with a beta-lactam antibiotic; commonly flucloxacillin or a cefalosporin, which whilst effective,[10] often leaves the patient with significant skin damage which takes many weeks to heal. Beta-lactams need a growing or dividing bacterium in order to work. Clindamycin, a protein inhibiting antibiotic, inhibits toxin production and is able to kill intracellular streptococci.[11, 12] It is these toxins which are responsible for local damage and systemic features.[13] Protein inhibiting antibiotics are part of recommended therapy for invasive GAS infections such as necrotising fasciitis and pleural empyema but there is conflicting evidence of any benefit[14, 15] and there are no clinical trials to support it. The evidence for an effect in reducing toxin has been predominantly in-vitro and even in-vitro studies show antagonism under some conditions,[16] but one retrospective and one prospective review showed benefit of clindamycin, in invasive infections caused by GAS.[17, 18]

Clindamycin is a recommended treatment for cellulitis in the British National Formulary;[19] it is a lincosamide and is also active against some macrolide (e.g. clarithromycin) resistant strains of streptococci and staphylococci. It was the second most common treatment for cellulitis in a survey of Canadian hospitals[20] and clindamycin or clarithromycin featured in every one of 23 guidelines examined as part of a review of treatment of cellulitis in the south west of England.[21] If clindamycin is an effective adjuvant in serious streptococcal infections, its benefit should be detectable in cellulitis. A reduction in toxin production should lead to a reduction in the severity of infection and result in less pain, more rapid resolution, improved short-term health-related quality of life, and a more rapid return to normal activity.

This trial was designed to determine whether clindamycin has an additional beneficial effect in cellulitis. Clear evidence that clindamycin has no benefit would have implications for the use of it as adjunctive or sequential therapy in cellulitis. Failure to demonstrate benefit would also suggest that the present recommendations for its use in invasive GAS infections need to be re-evaluated.
METHODS

Trial design and participants

We conducted a double-blind, randomised, placebo-controlled trial from October 2013 to December 2015, with 1:1 parallel group allocation. Potential participants were screened from emergency departments, hospital inpatients and referrals to hospital from general practice (family physicians) from 20 hospitals in England.

The diagnosis of cellulitis was supported using a set of criteria established for the PATCH trials on the prevention of recurrent cellulitis.[22] All adult patients with unilateral limb cellulitis were eligible; the key exclusion criteria were antibiotic treatment for longer than 48 hours, previous *Clostridium difficile* infection, past MRSA carriage, allergy to either penicillin or clindamycin (self-reported or from their medical records) and pre-existing diarrhoea. Patients with obvious abscesses were not eligible. We collected data on randomised and non-randomised participants as specified by CONSORT (Figure).

All participants were given flucloxacillin orally or intravenously, the dose and route was decided by the clinical team treating the patient. The minimum dose and duration of flucloxacillin specified in the protocol was 500mg four times per day orally for five days. Participants on other beta-lactams prior to recruitment, e.g. co-amoxiclav, were switched to flucloxacillin.

The dose of clindamycin in this trial was 300mg four times per day orally, which has been used in a large trial of skin and soft tissue infections,[23] and the duration was two days. The duration was designed to achieve adequate tissue levels of clindamycin whilst minimising the side effects. The protocol specified that clindamycin or placebo was to be started within 48 hours of starting the beta-lactam. This period was a compromise between giving the patient adequate time to consider the trial and minimise the duration of any preceding beta-lactam antibiotic, which might reduce any effect of clindamycin.

Randomisation and masking

Randomisation was web-based with blocks of 8 and stratified by age (<65 and >64) and part of the week to allow for variation in follow-up caused by weekends. The randomisation system provided a study number and study drug bottle number. Study medication was prepared and dispensed by the University Hospitals Bristol Pharmacy which provided batches of the medication bottles to the study sites. Both clindamycin and placebo were formulated and supplied in identical capsules sealed in identical medication bottles. Only the pharmacy kept the code of whether the bottle contained clindamycin or placebo. The pharmacy had no access to the clinical data or patient identification unless unblinding was required. The study nurses, the statistician, and all investigators and participants were blind to whether the bottle contained clindamycin or placebo.

Procedures

The study schedule consisted of three face-to-face visits, at Baseline, Day 5 and Day 10, with a telephone follow-up at Day 30. At the first three visits we measured standard observations (temperature, pulse, blood pressure and respiration rate). We also took blood for a full blood count, renal function, C-reactive protein and albumin. We estimated the affected skin area of the limb using...
a scoring system similar to that used in psoriasis[24] from which we calculated the percentage of body skin area. We measured the limb circumference at its greatest over the affected area and the highest temperature from the affected area and took comparable measurements from the unaffected limb, if available. The temperature measurements were made with an infra-red thermometer,[25] limb circumference with a disposable tape-measure and pain scores were measured using a visual analogue scale (VAS). A record of adverse events was made at each visit. The actual number of days after randomisation on which follow-up occurred was variable. The day of follow-up was dependent on the patients’ circumstances and, rather than lose a patient to follow-up, we asked patients to attend whenever they could, whilst still maintaining the target of four days post randomisation. We asked patients to return the study drug containers and counted remaining capsules.

We collected additional information, including Euroqol (EQ-5D-5L) and Health Today scores, at Baseline and Day 30 for a health economics analysis. We asked patients at each visit and at the Day 30 telephone follow-up whether or not they considered themselves to be back to their normal activities. At Baseline we recorded the time between the onset of systemic features, if reported, and local features. We recorded the time that antibiotics were first taken. We asked the patients about previous surgery, trauma or cellulitis of the affected limb and whether they had been diagnosed as having lymphoedema or diabetes mellitus as these are recognised risk factors.[26]

Outcomes

The primary outcome was improvement at the Day 5 follow-up visit. This was defined in the protocol, as being afebrile (<37.5°C) and either having a reduction in limb swelling (measured by limb circumference) or a reduction in erythema (measured by skin-surface temperature) of 0.2 standard deviations or more for both local measurements. The reduction in limb swelling and limb temperature was determined using the difference between affected and unaffected limbs to reduce confounding by ambient temperature, clothing and posture. These three clinical features were chosen because they could be measured accurately. 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.

Statistics

The estimated number improving in the placebo group at first follow-up was 80%. A two group continuity corrected chi-squared test with a 0.05 two-sided significance level will have 80% power to detect the difference between 80% improving in the placebo group and 90% improving in the clindamycin group (odds ratio of 2.250 ) when the sample size with complete data in each group is 219 (total 438). We were not able to make any estimates of the recruitment rate and likely losses to follow up as there was no suitable source of data; the only UK trial of cellulitis in an emergency department (the primary source of patients for this study) was reported in 2005 and used parenteral antibiotics.[27]

Confirmation of the determination of the primary outcome was made by the Trial Steering Group during the trial. There was no interim analysis and there were no pre-specified sub-group analyses.
The decision to undertake sub-group analyses was made after the analysis of the primary outcome. The trial was stopped at 26 months, with 410 patients randomised, for funding reasons.

Data was analysed on an intention to treat basis. A Fishers exact test, with odds ratios (OR), was used to determine whether there was a difference in those improving in each group at first follow-up (Day 5). The analysis of the secondary outcomes adjusted for some baseline imbalances between the treatment allocations (namely baseline total affected area, difference between baseline affected and unaffected limb temperature, difference between baseline affected and unaffected limb circumferences and the logarithm of neutrophil count). The analysis of the primary outcome was also repeated adjusting for these factors. Continuous outcomes were analysed using analysis of covariance (ANCOVA) and also adjusted for the baseline value of the outcome as well as the baseline imbalances. For dichotomous outcomes, logistic regression analysis was used to compare the adjusted odds of the outcome by treatment group. For continuous outcomes, there were some occasions where the distribution of the data was such that the logarithm of the outcome was used in the ANCOVA and there were also a few occasions when the assumptions for the ANCOVA were not met so it was necessary to use a Mann-Whitney test to compare the allocations. Medians have been reported instead of means where the data is markedly skewed.

PATIENT INVOLVEMENT

Patients were not involved in designing the study apart from the patient information sheet. We used qualitative study data collected previously, which highlighted patient comfort as important, to inform the choice of outcomes.[28, 29] The Day 30 telephone consultation asked for feedback and comments on the conduct of the study. Towards the end of the study we arranged a meeting and an on-line survey focusing on patients’ symptoms and non-pharmacological interventions.

RESULTS

Baseline

2444 patients with a diagnosis of cellulitis were screened for eligibility. 410 patients were randomised, ranging from 18 to 95 years. Nine patients were subsequently found to be ineligible because they had received more than 48 hours of antibiotics (5 patients) or the diagnosis was incorrect (4 patients). The flow chart (Figure) summarises the numbers of patients screened for eligibility and numbers present at each follow-up. All patients randomised are included in the intention to treat (ITT) population. The baseline characteristics of the randomised patients are summarised in Table 1; not every patient had a complete set of baseline data. The clindamycin allocation patients were slightly younger and had less severe cellulitis. Overall 55 (13%) patients had a history of previous surgery, 63 (15%) of trauma to and 132 (32%) of cellulitis of the affected limb. Nineteen (5%) had a diagnosis of lymphoedema and 36 (9%) of diabetes mellitus.

Withdrawal from the study and non-attendance at Day 5

Overall 48 patients were actively withdrawn from the study either at their own request or their physician’s; 27 in the clindamycin and 21 in the placebo allocation.

Six patients were found to be ineligible immediately after randomisation and did not receive the study drug (5 clindamycin and 1 placebo). The most common reason for active withdrawal from the
study was that the patient was given open label clindamycin either unintentionally (4 patients) or intentionally (14 patients); 9 in each allocation. One of these patients was unblinded, the only one from the trial, at the request of the clinical team. Four patients had the diagnosis changed; 3 in the clindamycin allocation. Three patients were withdrawn because of an adverse event; one in the clindamycin allocation. Eleven patients withdrew their consent; 8 in the clindamycin allocation. Seven patients withdrew for other reasons; 3 in the clindamycin allocation. Four patients given open label clindamycin before Day 5 are included in the analysis of primary outcome; two in the clindamycin allocation and two in the placebo allocation.

We looked at the baseline characteristics of those patients who did not attend the Day 5 follow-up and compared them with those that did by univariate analysis. We found that the non-attendees, as a group, were significantly younger; the mean age of attendees was 50.8 and non-attendees was 41.4 years (P < 0.001) Attendees were significantly more likely to have leg cellulitis than non-attendees; 76% versus 62% (P= 0.02). Attendees were less likely to have a SIRS score ≥1; 41% versus 59% of non-attendees (P= 0.006). There were no differences in the baseline characteristics of the non-attendees between the study drug allocations.

**Primary outcome and Day 5 follow-up**

We were able to calculate the primary outcome for 328 patients. To be evaluable, patients had to have a body temperature measurement and a measurement of either limb circumference or limb surface temperature. Those with missing data on temperature at Day 5, or the three with missing unaffected limb data, were categorised as having missing data for primary outcome. Patients with temperature data, but with missing data on both limb circumference and limb temperature, were categorised as not improved, rather than missing. Patients with temperature data, and with either a measure for change in circumference or change in limb temperature, were categorised according to the two out of three data items they had available. The median number of days to follow-up was 4.0 for clindamycin and 4.1 for placebo.

Within the evaluable population there was no significant difference in improvement which was 87% for clindamycin and 81% for placebo; OR 1.55 (95% CI 0.81 to 3.01), p=0.17 (Table 2). Adjusting for baseline differences did not alter the primary outcome result. As a proportion of those patients randomised improvement occurred in 67% of those on clindamycin compared to 68% those on placebo; OR 0.97 (95% CI 0.63 to 1.50), p=0.92.

**Route, dose and duration of flucloxacillin**

The quality of the data on the duration and route of flucloxacillin during the trial was poor. We had not set out to collect data on dose because we assumed a standard dose of oral flucloxacillin but we later discovered that some hospitals used higher doses. Consequently, we have not included this in any of the analyses presented here.

**Sub-group analyses**

We did not specify any sub-group analysis in the study protocol but in order to clarify whether there might have been a positive effect from clindamycin in a sub-population and a negative, or neutral effect, in another sub-population we undertook sub-group analyses. We looked at severity as defined as having a systemic inflammatory response syndrome (SIRS) score of zero or more than
zero; duration of local features (area, skin temperature and swelling) of between 48 and 84 hours, or less than 48 hours prior to randomisation; duration of antibiotics prior to the study drug of greater or less than 12 hours. No statistically significant difference in improvement in any sub-group was found.

Compliance

The majority of the study drugs were taken; 148/159 (93%) in the clindamycin group and 159/176 (90%) of the placebo group had zero capsules remaining. The mean number of capsules remaining of the 11/159 in the clindamycin allocation was 6.5 and of the 17/176 in the placebo allocation was 4.4 out of 16 capsules.

Day 10 follow-up and secondary outcomes

Fifty-four patients who attended at Day 5 did not attend at Day 10. The non-attendees were younger but otherwise similar to those that attended Day 5. There was no significant difference in any secondary outcome measures except a slightly lower mean blood pressure (systolic, 3 mm Hg) in the clindamycin allocation at Day 10 and lower median lymphocyte counts in the clindamycin allocation at both Day 5 and Day 10 (0.18 and 0.19 X 10^9/L respectively). The median number of days to follow-up was 9 days in both allocations. Table 3 summarises the secondary outcomes at Day 5 and at Day 10.

Back to normal activities

At Day 5 76/158 (48%) of the clindamycin allocation were back to normal activities compared to 74/175 (42%) of the placebo allocation (OR 1.09 (CI 0.66 to 1.78), p=0.74). At Day 10 77/133 (58%) of the clindamycin allocation were back to normal activities compared to 82/153 (54%) of the placebo allocation (OR 1.13 (CI 0.67 to 1.89), p=0.65). At the Day 30 follow up the median duration from recruitment was 38.4 days in both allocations. Two hundred and fifty patients had a response to the question on their return to normal activities; 99/121 (82%) in the clindamycin allocation were back to normal activities compared to 104/129 (81%) in the placebo allocation (OR 0.90 (95% CI 0.44 to 1.84), p=0.77). The odds ratios are adjusted odds ratios adjusting for total affected area, difference in limb circumference, difference in limb temperature and neutrophil at baseline.

Adverse events

Diarrhoea was the most common adverse event in the clindamycin allocation with 34/158 (22%) of the clindamycin allocation reporting it compared to 16/172 (9%) in the placebo allocation (OR 2.7 (95% CI 1.41 to 5.07), p=0.002) (Table 4). Adverse events resulted in three patients leaving the trial before Day 5. Any hospital admission, for any reason, after recruitment and during the first 10 days of follow-up was recorded as a serious adverse event (SAE). There were 23 SAE (8 in the clindamycin allocation and 15 in the placebo allocation) and none were thought to be related to their study drug treatment. No case of *Clostridium difficile* infection was reported. Two patients died before Day 30 and of causes unrelated to cellulitis or their treatment (one myocardial infarction and one pulmonary embolus) both were in the placebo allocation.

DISCUSSION

DRAFT 4 submission
The results of this clinical trial do not provide evidence that any feature of cellulitis was improved by the addition of clindamycin. We collected a wide array of objective data in order to detect particular effects of clindamycin which might be related to toxin production and none showed any effect. The range of severity in the study patients was wide; we included those both on oral and intravenous flucloxacillin therapy. We looked to see whether clindamycin’s effects may be only evident in those with more severe disease, in those who had a shorter duration of features or those who had antibiotic treatment earlier. We could find no evidence that any of these circumstances made the addition of clindamycin beneficial. However, we did find that the proportion of patients in the clindamycin allocation with diarrhoea, up to Day 5, was double that of the patients receiving placebo.

This study has some weaknesses; about 20% of patients did not attend the first follow up but this is a feature of an acute infection which, in many people heals rapidly, and of the population attending emergency departments. We were unable to find any significant differences in attendance between the two study allocations that could not be accounted for by the marginal differences in severity. We were unsure of what duration we should allow between initial antibiotic therapy and clindamycin but we could find no significant difference in outcome when we compared those having started antibiotics within 12 hours with those between 12 and 48 hours. We were also uncertain about the appropriate duration of clindamycin to detect an effect if it was present. We did detect an effect, an adverse one; diarrhoea, with the 48 hour duration.

This study was developed as a result of a south west England regional review of treatment of proven group A streptococcal (GAS) infection which was undertaken in 2011. As part of this review we could find no evidence of benefit of the addition of clindamycin despite its widespread and increasing use. This led us to look at a way of testing the hypothesis that clindamycin’s protein-inhibiting activity is of benefit in GAS infection. There had been no previous studies on adjunctive clindamycin in cellulitis and we thought this study would be helpful both in the management of cellulitis and invasive GAS infections. This study was designed to test the hypothesis that a toxin-inhibiting antibiotic, of which clindamycin is the exemplar, is effective in streptococcal infections. Cellulitis is a common streptococcal infection with easy-to-measure objective features and has been used in this trial as a representative streptococcal infection. We think it is reasonable to generalise the results of this trial to other streptococcal infections in the absence of specific trials.

The in-vitro evidence that supported clindamycin’s benefits is conflicting and the clinical evidence of benefit in invasive GAS infections has the biases intrinsic in these retrospective and prospective studies:[17, 18] patient selection, patient treatment, recall and publication. The principal reason for the unsupported use of clindamycin in cellulitis is a widespread misunderstanding of the natural history of the condition. The local features of cellulitis will often progress (or at least not improve) for several days after presentation. An increasing affected area with mild fever and rising CRP leads both patient and physician to believe that the antibiotic treatment is failing; this is despite the patient’s systemic symptoms of rigors, nausea and anorexia improving. The addition of clindamycin or change to intravenous therapy is consequently and spuriously attributed as being responsible for the patient’s improvement. The fact that 16 patients were intentionally given clindamycin and withdrawn from the trial is a reflection of the belief in clindamycin’s powers. It is probable that by the time the patient presents to a healthcare professional with local signs of cellulitis the various toxins have bound to their targets and initiated the exaggerated inflammatory response which is
part of the cause of skin damage. At this point the streptococcus is replicating and susceptible to beta-lactam antibiotics, or no longer viable, so the addition of another antibiotic will have no beneficial effect. The mechanisms are similar to those of envenoming[30] and it is unsurprising that drugs thought to reduce toxin production given days later are unlikely to be effective.

The Cochrane review of interventions in cellulitis found no difference in outcome, however measured, between treatment with a beta-lactam versus either macrolides or streptogramin.[10] A large trial comparing dicloxacillin with clindamycin in the treatment of skin infections found no difference in efficacy.[23] These studies support the outcome of this trial; because if toxin inhibition was of importance then the superiority of clindamycin should have been evident.

This clinical trial has shown that adjunctive clindamycin has no effect on improving outcome in cellulitis. Its only real effect is increasing the likelihood of diarrhoea with a rate comparable to that previously recorded.[23, 31] It also is likely that there is no benefit in invasive GAS disease. Any further use of adjunctive clindamycin and other protein-inhibiting antibiotics, either concurrently or sequentially, for the treatment of streptococcal and staphylococcal infections should only be within a clinical trial.
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Hazel Taylor, Research Design Service South West; statistical advice and data analysis

Kim Thomas and Katharine Foster, Centre of Evidence Based Dermatology; trial design and documentation

The following principal investigators and lead research nurses:

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Trial steering committee

The trial steering committee was chaired by Richard Gray with Tristan Clark and Richard Thomson.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: the study was funded by the UK National Institute for Health Research’s (NIHR) Research for Patient Benefit (RfPB) programme; no financial relationship with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

CONTRIBUTORS

RB conceived the concept, designed and supervised the study. RB and OMW analysed and interpreted the data. RB and PF drafted the manuscript. PD, TH and HJ all contributed to data collection. ADH contributed to the design and methodology. All authors were involved in data interpretation, contributed to, and approval of, the final manuscript.

RB is the guarantor
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ETHICAL APPROVAL

The trial was approved by the UK National Research Ethics Service (reference number: 13/SC/0211) and informed consent was obtained from all participants.

TRANSPARENCY

The authors affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

DATA SHARING AND TRIAL PROTOCOL

Anonymised patient level data are available on reasonable request from the corresponding author. The full trial protocol is available from the corresponding author.

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

<table>
<thead>
<tr>
<th></th>
<th>Clindamycin (n=203)</th>
<th>Placebo (n=207)</th>
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<tbody>
<tr>
<td>Mean (SD) age in years</td>
<td>47.7 (18.4)</td>
<td>50.5 (16.9)</td>
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<tr>
<td>Male</td>
<td>129 (64)</td>
<td>149 (72)</td>
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<tr>
<td>Leg affected</td>
<td>150 (74)</td>
<td>149 (72)</td>
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<tr>
<td>Duration of local features before starting study drug (days); Median (IQR)</td>
<td>2.1 (2.1)</td>
<td>2.0 (2.1)</td>
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<td>Duration of preceding antibiotics before starting study drug (hours); Median (IQR)</td>
<td>1.9 (19.0)</td>
<td>6.5 (23.5)</td>
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<td>Temperature (°C); Mean (SD)</td>
<td>36.8 (0.5)</td>
<td>36.9 (0.7)</td>
</tr>
<tr>
<td>Pulse (beats per minute); Mean (SD)</td>
<td>81 (15)</td>
<td>81 (14)</td>
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<td>Systolic blood pressure (mm Hg); Mean (SD)</td>
<td>131 (20)</td>
<td>128 (18)</td>
</tr>
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<td>Affected skin area as percentage of body surface area; Median and IQR</td>
<td>4 (4)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Difference in circumference between affected and unaffected limb (cm); Mean (SD)</td>
<td>2.5 (2.1)</td>
<td>2.9 (2.1)</td>
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<td>Difference in surface temperature between affected and unaffected limb (°C); Mean (SD)</td>
<td>2.5 (1.9)</td>
<td>2.7 (1.6)</td>
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<td>6.3 (4.6)</td>
<td>7.0 (4.9)</td>
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<td>1.6 (0.7)</td>
<td>1.5 (1.1)</td>
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<td>Urea (mmol/L); Median (IQR)</td>
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<td>4.9 (2.1)</td>
</tr>
<tr>
<td>Albumin (g/L); Median (IQR)</td>
<td>39 (7)</td>
<td>38 (8)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L); Median (IQR)</td>
<td>23 (80)</td>
<td>54 (119)</td>
</tr>
<tr>
<td>Pain score (VAS); Median (IQR)</td>
<td>5 (4)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>SIRS score ≥1*</td>
<td>83/200 (42)</td>
<td>96/207 (46)</td>
</tr>
</tbody>
</table>

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 (WBC count derived from neutrophils plus lymphocytes plus 1)
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)

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

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)

<table>
<thead>
<tr>
<th></th>
<th>Time point</th>
<th>Clindamycin</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C); Mean</td>
<td>Baseline</td>
<td>36.8</td>
<td>36.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>36.6</td>
<td>36.5</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>36.5</td>
<td>36.5</td>
<td>0.74</td>
</tr>
<tr>
<td>Pulse (beats per minute); Mean</td>
<td>Baseline</td>
<td>80</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>78</td>
<td>76</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>78</td>
<td>77</td>
<td>0.76</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg); Mean</td>
<td>Baseline</td>
<td>131</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>129</td>
<td>131</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>128</td>
<td>131</td>
<td>0.02</td>
</tr>
<tr>
<td>Affected skin area as percentage of body surface area; Median</td>
<td>Baseline</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>2</td>
<td>2</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>1</td>
<td>1</td>
<td>0.67</td>
</tr>
<tr>
<td>Difference in circumference between affected and unaffected limb (cm); Mean</td>
<td>Baseline</td>
<td>2.67</td>
<td>2.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>2.04</td>
<td>2.18</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>1.42</td>
<td>1.77</td>
<td>0.90</td>
</tr>
<tr>
<td>Difference in surface temperature between affected and unaffected limb (°C); Mean</td>
<td>Baseline</td>
<td>2.49</td>
<td>2.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>1.15</td>
<td>1.57</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>0.87</td>
<td>1.13</td>
<td>0.65</td>
</tr>
<tr>
<td>Neutrophil (X (10^9)/L); Median</td>
<td>Baseline</td>
<td>5.97</td>
<td>6.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>4.24</td>
<td>4.43</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>4.18</td>
<td>4.32</td>
<td>0.86</td>
</tr>
<tr>
<td>Lymphocyte (X (10^9)/L); Median</td>
<td>Baseline</td>
<td>1.51</td>
<td>1.50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>1.70</td>
<td>1.88</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>1.75</td>
<td>1.94</td>
<td>0.01</td>
</tr>
<tr>
<td>Urea (mmol/L); Median</td>
<td>Baseline</td>
<td>5.0</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>4.8</td>
<td>5.0</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>4.9</td>
<td>5.2</td>
<td>0.37</td>
</tr>
<tr>
<td>Albumin (g/L); Median</td>
<td>Baseline</td>
<td>38</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>38</td>
<td>37</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>39</td>
<td>38</td>
<td>0.63</td>
</tr>
<tr>
<td>C-reactive protein (mg/L); Median</td>
<td>Baseline</td>
<td>22</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>10</td>
<td>16</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>5</td>
<td>6</td>
<td>0.20</td>
</tr>
<tr>
<td>Pain score (VAS); Median</td>
<td>Baseline</td>
<td>4.5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>2</td>
<td>2</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>Day 10</td>
<td>0</td>
<td>1</td>
<td>0.61</td>
</tr>
</tbody>
</table>

The baseline values are of those patients who attended Day 5. The baseline values for those attending Day 10 are similar to the Day 5 baseline values.

All p-values are from ANCOVA (adjusted for baseline) except for pain VAS score at day 5 (Mann Whitney U Test).
Table 4. Adverse events or reactions. Figures are numbers of patients with an adverse reaction or event (percentage)

<table>
<thead>
<tr>
<th></th>
<th>Clindamycin</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reported at Day 5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>3 (1.9)</td>
<td>8 (4.6)</td>
<td>0.22</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>34 (21.5)</td>
<td>16 (9.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Any adverse event (including rash and diarrhoea)*</td>
<td>46 (28.9)</td>
<td>27 (15.6)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Reported at Day 10</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2 (1.5)</td>
<td>10 (6.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>17 (12.8)</td>
<td>8 (5.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Any adverse event (including rash and diarrhoea)*</td>
<td>19 (14.1)</td>
<td>19(12.6)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

*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.
Flow chart summarising the numbers of patients screened for eligibility and numbers present at each follow-up.

The flow chart (Figure)

184x229mm (96 x 96 DPI)
C4C Trial CONSORT 2010 checklist of information to include *

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1a</td>
<td>Identification as a randomised trial in the title</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>Structured summary of trial design, methods, results, and conclusions</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(for specific guidance see CONSORT for abstracts)</em></td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
<td>5</td>
</tr>
<tr>
<td>Methods</td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
<td>N/A</td>
</tr>
<tr>
<td>Participants</td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
<td>6</td>
</tr>
<tr>
<td>Interventions</td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td>6</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
<td>N/A</td>
</tr>
<tr>
<td>Sample size</td>
<td>7a</td>
<td>How sample size was determined</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
<td>N/A</td>
</tr>
<tr>
<td>Randomisation:</td>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8b</td>
<td>Type of randomisation; details of any restriction (such as blocking and block size)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those</td>
<td>6</td>
</tr>
</tbody>
</table>
11b If relevant, description of the similarity of interventions

### Statistical methods
- 12a Statistical methods used to compare groups for primary and secondary outcomes
- 12b Methods for additional analyses, such as subgroup analyses and adjusted analyses

### Results
**Participant flow (a diagram is strongly recommended)**
- 13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
- 13b For each group, losses and exclusions after randomisation, together with reasons

**Recruitment**
- 14a Dates defining the periods of recruitment and follow-up
- 14b Why the trial ended or was stopped

**Baseline data**
- 15 A table showing baseline demographic and clinical characteristics for each group

**Numbers analysed**
- 16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

**Outcomes and estimation**
- 17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
- 17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended

**Ancillary analyses**
- 18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory

**Harms**
- 19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)

### Discussion
**Limitations**
- 20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses

**Generalisability**
- 21 Generalisability (external validity, applicability) of the trial findings

**Interpretation**
- 22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

### Other information
**Registration**
- 23 Registration number and name of trial registry

**Protocol**
- 24 Where the full trial protocol can be accessed, if available

**Funding**
- 25 Sources of funding and other support (such as supply of drugs), role of funders

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.*

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CONSORT 2010 checklist

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Adjunctive clindamycin for cellulitis: a clinical trial comparing flucloxacillin with or without clindamycin for the treatment of limb cellulitis

Richard Brindle, O Martin Williams, Paul Davies, Tim Harris, Heather Jarman, Alastair D Hay and Peter Featherstone

**BMJ Open** 2017 7:
doi: 10.1136/bmjopen-2016-013260

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