

A randomised placebo-controlled trial of oral and topical antibiotics for children with clinically infected eczema in the community: the ChildRen with Eczema, Antibiotic Management (CREAM) study

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Scientific summary

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Scientific summary

Background

Eczema affects approximately 20% of children in the UK. Eczema is a relapsing–remitting condition and a significant proportion of eczema flares will be treated with antibiotics. *Staphylococcus aureus* has long been known to be more prevalent on the skin of patients with eczema, and is found in higher densities in people with more severe eczema. This has led to a wide range of therapies and products intended to reduce the presence of *S. aureus* with the aim of reducing the severity and frequency of eczema flares. However, evidence for the effectiveness of these interventions is limited. A Cochrane systematic review published in 2008 (and an update published by the same authors in 2010) found that most studies were small and at high risk of bias, and that the results were conflicting. Only three previous studies have evaluated the effects of oral antibiotics in eczema, and only one of these (33 children) involved clinically infected eczema, and this found no significant difference in eczema severity at follow-up. There was a similar lack of clear evidence with regard to topical antibiotics, or indeed any antimicrobial agents, leading the authors of the review to conclude that ‘Their continued use should be questioned in such situations, until better and longer-term studies show clear evidence of clinical benefit’ (Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, Williams HC. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema: an updated Cochrane review. *Br J Dermatol* 2010;**163**:12–26).

This is important not only because of the need to identify effective treatments for children with eczema, but also to reduce the use of ineffective treatments currently being prescribed. Widespread use of antimicrobials contributes to the development of antimicrobial resistance and exposes children to possible harms from adverse effects, so it is justifiable only where there is clear evidence of benefit.

Objectives

The main aim of this study was to evaluate the clinical effectiveness of oral and topical antibiotics in children in the community with clinically suspected infected eczema. The objectives were to assess the effects of oral and topical antibiotics, in addition to standard treatment with emollients and topical corticosteroids (TCSs), on:

- short-term (2 weeks) subjective eczema severity (primary)
- longer-term (4 weeks and 3 months) subjective eczema severity
- short- and longer-term objective eczema severity
- impact on the family, quality of life and daily symptoms.

In addition to:

- comparing oral and topical antibiotic treatments in terms of short- and long-term effects, adverse effects, parent preference and effect on prevalence of colonisation/infection with resistant organisms
- validating a new condition-specific preference-based measure of health for children
- describing the prevalence of antibiotic resistance in isolates at baseline and follow-up in those who received oral and topical antibiotics and placebo.

Methods

We undertook a multicentre, double-blinded, individually randomised, placebo-controlled trial in general practices and dermatology clinics in England, Wales and Scotland. A total of 91 general practices and 4 dermatology clinics participated, of which 32 (35%) and one (25%), respectively, recruited participants. Clinicians in participating centres opportunistically identified children (aged 3 months to < 8 years) consulting who had eczema (as defined by U.K. Working Party) that was clinically suspected of being infected. Recent use of antibiotics (past week) or (very) potent TCSs (2 days), suspected eczema herpeticum, significant comorbid illness, severe infection and allergy to study medication were all exclusion criteria. Eligible children were then seen by a research nurse within the next 72 hours for further eligibility assessment, provision of informed consent, baseline data collection and provision of study medication. Participants were randomised to one of three study arms: oral antibiotic and topical placebo (oral antibiotic); topical antibiotic and oral placebo (topical antibiotic); or oral and topical placebos (control). Randomisation was conducted by study pharmacies using pre-prepared allocation lists using block randomisation stratified by site and penicillin allergy status. Study medication packs were identical (with taste- and colour-matched placebos). Participants, research nurses and clinical team were blinded to the allocation. The interventions under evaluation were flucloxacillin suspension or erythromycin suspension for those with penicillin allergy (dose according to age according to *British National Formulary* guidance), and fusidic acid cream (Fucidin®, Leo Laboratories Limited), applied three times a day, all for 1 week. In addition, all children were prescribed hydrocortisone 1% for use on the face and clobetastone butyrate 0.05% (or another moderate-strength TCS) for use on other parts of the body.

Outcomes were measured at 2 and 4 weeks via visits from a research nurse and at 3 months via a postal questionnaire and swabs. In addition, we conducted a review of each patient's primary care medical record for the 3 months following randomisation. The primary outcome was a comparison of Patient-Orientated Eczema Measure (POEM; assesses subjective eczema severity over the preceding week) at 2 weeks between each active intervention group and the control (placebo/placebo) group. Other outcomes included objective eczema measured using the Eczema Area and Severity Index (EASI), family impact using the Dermatitis Family Impact instrument, quality of life using the Infant's Dermatology Quality of Life instrument or the Children's Dermatology Life Quality Index, health utility status using a new preference-based disease-specific measure [Atopic Dermatitis Quality of Life Index (ADQoL)], daily symptoms, medication use, adverse effects, parental views about treatment, consultations and microbiology (presence of *S. aureus* and β -haemolytic streptococci on the skin and in the nose and mouth at baseline, 2 weeks and 3 months, and resistance in isolates at each time point).

We planned to recruit 137 participants per treatment arm to have 90% power to detect difference of 3 in POEM scores. After 9 months of recruitment at a slower than anticipated rate, we used data from the first 69 participants to check the assumptions of the sample size calculation. This resulted in us using a smaller standard deviation (SD) for baseline POEM (SD 5.3) and a correlation between baseline and week 2 POEM scores (SD 0.27) that resulted in an amended sample size calculation of 94 patients per arm. After 113 patients had been recruited a decision was made by the Health Technology Assessment programme to terminate the trial early due to slow recruitment.

Results

We randomised 113 children (36 to oral antibiotic, 37 to topical antibiotic and 40 to placebo). Four children were recruited from dermatology clinics, the rest from primary care. Only three children had penicillin allergy, and none of these was randomised to the oral antibiotic arm, so no child received active oral erythromycin. We were able to follow up 101 (89.4%) children at 2 weeks, 98 (86.7%) at 4 weeks and 74 (65.5%) at 3 months, and conduct a 3-month notes review for 97 (85.8%) participants.

Participants had a mean age of 3.1 (SD 2.1) years, 54% were female, 80.5% were white, 74.6% had a flare that had lasted for ≤ 14 days and 92.0% reported having one or more of weeping, crusting, pustules or painful skin as a symptom at baseline. One hundred participants had their clinical features recorded objectively by a research nurse (47 by photographs and 53 by completing a questionnaire directly while examining the patient). Of these, 30.0%, 10.1%, 6.8% and 53.0% had moderate or severe crusting, weeping, pustules or erythema, respectively.

Mean baseline POEM scores were 13.42, 14.62 and 16.90 in the control, oral antibiotic and topical antibiotic groups, respectively. POEM scores at 2 weeks after correcting for baseline scores were higher (worse severity) in the oral antibiotic and topical antibiotic groups by 1.52 [95% confidence interval (CI) -1.35 to 4.40] and 1.49 (95% CI -1.55 to 4.53) than in the control group. The lower bands of the CIs (-1.35 and -1.55) are less than the published minimal clinically important difference for POEM of 3.0, and therefore these results suggest that the interventions do not result in clinically meaningful benefit in this population. EASI (objective severity) scores were also higher (worse) in the intervention groups [by 0.20 (95% CI -0.12 to 0.52) and 0.42 (95% CI 0.09 to 0.75) for oral and topical antibiotics, respectively] at 2 weeks. Analyses of impact on the family, quality of life, daily symptom scores, and longer-term outcomes were all consistent with the finding of no or limited difference and a trend towards worse outcomes in the intervention groups. Daily total symptom scores improved over the first 7 days and then stabilised in all three groups. There was no difference in area under the curve between the three groups.

Culture of baseline skin swabs resulted in isolation of *S. aureus* from 69.6% of patients. By 2 weeks and 3 months this had reduced to 44.4% (95% CI 34.5% to 54.4%) and 36.1% (95% CI 24.7% to 47.5%), respectively. Less than 10% of isolates were resistant to flucloxacillin at all time points and in all groups. A total of 26.9% of *S. aureus* isolates from the skin were resistant to fusidic acid at baseline. This had increased to 31.1% overall (and 72.7% in the topical antibiotic group) by 2 weeks but decreased to 15.4% overall by 3 months.

There were no significant between-group differences in reported adverse effects. New rash (17.5%) and diarrhoea (15.5%) were the most commonly reported adverse events.

Overall, participants reported taking 61.3% of oral antibiotic (or matched placebo) doses and using 81.8% of topical antibiotic (or matched placebo) applications. A complier-average casual effect analysis to adjust for adherence produced results that were very similar to the main analysis. During the first 2 weeks, 55 patients used hydrocortisone 1% and 70 patients used clobetastone butyrate 0.05% (or another moderate-strength TCS). Participants applied a mean of 7.5 (SD 5.4) and 7.1 (SD 3.6) applications per week, respectively, and there were no significant differences between groups. During the 3-month follow-up period, 74% and 11% of participants reported one or more primary care and secondary care consultations, respectively.

Sensitivity analyses, including adjusting for region and imputing missing data, produced similar results to the main analyses. A post-hoc subgroup analysis by presence of *S. aureus* on the skin or not found evidence of harm or no effect in those with *S. aureus* [increase in POEM of 2.20 (95% CI -1.06 to 5.50) and 1.79 (95% CI -1.67 to 5.25) for oral and topical antibiotics, respectively] and wide CIs that included benefit, no effect and harm in those with negative cultures.

Most parents reported that the ADQoL was easy to answer and reflected the impact of eczema on their child. Some parents of younger children found it difficult to answer, and other parents would have liked additional response options to accommodate health status in between those currently presented in the questionnaire. Correlations with other health outcome measures used in the study were significant, in the right direction and of moderate strength. The instrument showed good discriminate validity at 2 weeks and sensitivity to change was moderate for the change between baseline and 2 weeks.

Conclusions

The ChildRen with Eczema, Antibiotic Management study is the largest trial to date to evaluate the effect of oral and topical antibiotic treatment for clinically infected eczema in children, and the only trial to be conducted in primary care, where most people with eczema are treated. We used pragmatic inclusion criteria, based around clinical suspicion of infection, and interventions that are commonly used in routine clinical practice. Although the study had to close before reaching its recruitment target, and the CIs around our main effect sizes include the null and are wider than if we had recruited to target, we have provided strong evidence of lack of meaningful clinical benefit from either oral or topical antibiotics in this population. One of the challenges that contributed to recruitment problems was the lack of a clear definition of infected eczema, and unclear equipoise among some clinicians and parents around the role of antibiotics in children with 'infected eczema'. For this reason, our results may not be able to be generalised to all children with suspected infected eczema. Nevertheless, all participants had clinically suspected infected eczema, and the majority had features classically associated with infection as well as a positive culture for *S. aureus*. Therefore, we believe that for the majority of patients seen in primary care with a clinical suspicion of infection, antibiotics can be safely withheld as long as adequate treatment with emollients and TCSs are provided and appropriate safety-netting is put in place.

Trial registration

This trial is registered as European Union Drug Regulating Authorities Clinical Trials (EudraCT) number 2011-003591-37 and International Standard Randomised Controlled Trial Number (ISRCTN) 96705420.

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