Antibiotics for infected eczema: the CREAM study

A small UK randomised controlled trial compared 7 days of oral flucloxacillin, topical fusidic acid and placebo in 113 children who had infected eczema. It was unable to recruit sufficient children and so did not have the power to consider the statistical significance of results. The primary outcome, a Patient-Oriented Eczema Measure (POEM) at 2 weeks, based on symptoms over the previous week, suggested oral or topical antibiotics had no effect or a worse effect. However, this needs to be interpreted in the context of the limitations. Notably, children with severe infection were specifically excluded and some children with ‘clear infection’ were not recruited to the study because either the clinician or parent was unhappy about them being in a trial that risked them receiving no antibiotic treatment. The NICE guideline on atopic eczema in under 12s restricts use of oral or topical antibiotics in children with infected eczema to no longer than 2 weeks.

Overview and current advice

Staphylococcus aureus is more prevalent on the skin of people who have eczema than on the skin those who do not have eczema and increased severity of eczema is associated with higher densities of the organism and more resistant strains. However, its exact role in the maintenance or exacerbation of eczema is unclear and there is currently not enough evidence to be sure whether topical or oral antibiotics are effective and safe for managing children with clinically infected eczema¹.

The NICE guideline on atopic eczema in under 12s recommends that children with atopic eczema and their parents or carers should be offered information on how to recognise the symptoms of bacterial infection with Staphylococcus and/or Streptococcus and how to access appropriate treatment if eczema becomes infected. In addition the guideline recommends:

- Systemic antibiotics that are active against S. aureus and Streptococcus should be used to treat widespread bacterial infections of atopic eczema in children for 1–2 weeks according to clinical response.
- Flucloxacillin should be used as the first-line treatment for bacterial infections in children with atopic eczema for both S. aureus and streptococcal infections. Erythromycin should be used in children who are allergic to flucloxacillin or in the case of flucloxacillin resistance. Clarithromycin should be used if erythromycin is not well tolerated.
- The use of topical antibiotics in children with atopic eczema, including those combined with topical corticosteroids, should be reserved for cases of clinical infection in localised areas and used for no longer than 2 weeks.
Recommendations are also given on the use of antiseptics in children who have recurrent infected atopic eczema and guidance on identification and management of eczema infected with the *Herpes simplex* virus, including eczema herpeticum (widespread herpes simplex virus). Healthcare professionals should only take swabs from infected lesions of atopic eczema in children if they suspect microorganisms other than *S. aureus* to be present, or if they think antibiotic resistance is relevant. After treatment for infected atopic eczema, products in open containers can become contaminated with microorganisms and act as a source of infection, therefore children and their parents or carers should be told to get new supplies.

The NICE pathway on [eczema](#) brings together all related NICE guidance and associated products on this condition in a set of interactive topic-based diagrams. See the Clinical knowledge summary information on [atopic eczema](#) for a general overview of prescribing considerations.

### New evidence

The UK double-blind, randomised controlled trial (RCT), *ChildRen with Eczema Antibiotic Management (CREAM) study* aimed to determine the clinical effectiveness and cost-effectiveness of the most commonly used oral and topical antibiotics, in addition to topical corticosteroids, in the management of clinically suspected infected eczema in children. In this RCT, 113 children (aged 3 months to under 8 years) were randomised to 1 of 3 treatment arms for 7 days:

- oral flucloxacillin four times a day at a standard dose for their age (or erythromycin if penicillin allergic) plus topical placebo (n=36)  
- topical 2% fusidic acid cream three times a day to the affected area plus oral placebo (n=37)  
- oral placebo plus topical placebo (n=40).

In addition, all participants were given topical corticosteroid treatment to use daily (hydrocortisone 1% for face and a moderate potency cream for trunk and/or limbs) for 14 days, were encouraged to use emollients (without antimicrobial agents) and received written and verbal instructions on eczema care. Participants came from 32 GP sites and 1 dermatology clinic, all had an eczema severity rating of 2 (‘slight problem’) or worse.

Clinically infected eczema was defined according to the [UK Working Party definition](#), but it could include children where eczema was failing to respond to standard treatment with emollients and/or mild to moderate topical corticosteroids, where there was a flare in the severity or extent of eczema, or where there was weeping and crusting. Children who had clinically severe infections or significant comorbid illnesses were excluded. Exclusion criteria also included children who had used oral or topical antibiotics to treat a skin infection within the past week and those who used potent or very potent topical corticosteroids within the past 2 days. Allocation was concealed. At baseline, 92% of children had at least one ‘classic’ sign of infection (weeping, crusting, pustules or painful skin), and 70% had *S. aureus* isolated from a skin swab (taken from all children at baseline).

The trial was stopped early due to low recruitment, which limited the power of the study, and the analysis estimated effect sizes and confidence intervals (CIs). The primary outcome was an assessment of subjective severity at 2 weeks, using the validated 28-point [Patient-Oriented Eczema Measure](#) (POEM), which is based on symptoms over the previous week (score increases with severity of eczema; minimum clinically important difference was considered to be 3.4). Data were available for 101 children (73% with and 27% without *S. aureus* isolated from a skin swab). At 2 weeks, the POEM had reduced from 13.42 to 6.17 in the control group, from 14.62 to 8.27 in the oral antibiotic group and from 16.90 to 9.32 in the topical antibiotic group. This showed an increased (worse) intervention effect compared with the control group of 1.52 (95% CI -1.35 to 4.40) from oral antibiotics and 1.49 (95% CI -1.55 to 4.53) from topical antibiotics. No clear benefit was found with topical or oral antibiotics in the POEM after 4 weeks or 3 months. Because the confidence intervals crossed zero, the authors highlighted that the data suggested oral and topical antibiotics have no effect or a worse effect on subjective eczema severity in children with clinically infected eczema in the community. No clinically
beneficial effect was found with oral or topical antibiotics when only 74 children with positive skin culture for *S. aureus* were considered.

There was no clinically beneficial effect found with oral or topical antibiotics in secondary outcomes such as subjective severity at 4 weeks, objective eczema severity at 2 and 4 weeks, quality of life, impact on the family and daily symptom scores. The authors were unable to exclude a clinically meaningful beneficial effect on subjective severity with topical antibiotics at 3 months. Overall, the authors concluded that this study provides the clearest evidence to date that neither topical nor oral antibiotics are likely to benefit children with mild clinically infected eczema.

**Commentary**

**Commentary provided by NICE**

This RCT is currently the largest published study of the effectiveness of oral and topical antibiotics in children with infected eczema. Its strengths also include that it was conducted in the UK, it used a patient-oriented outcome and the antibiotics included in the study (oral flucloxacillin and topical fusidic acid) are commonly used in routine practice. However, the most significant challenge to this study was its failure to recruit sufficient children with clinically infected eczema and so it did not have the power to analyse the results in terms of statistical significance. Even so, the confidence intervals crossed zero and, in most cases for the POEM, the lower band of the 95% CIs was less than the minimum clinically important difference of 3.4 that has been published in one study, suggesting oral and topical antibiotics have no effect or a worse effect in children with infected eczema. The findings from the secondary endpoints were generally consistent with this. The authors also commented that the results are largely consistent with previous, smaller and less rigorous studies in this area. Due to the low recruitment numbers, the full health economic evaluation that was originally planned could not be carried out.

It is necessary to consider this study in the context of some important limitations. The authors point out that the recruitment problems were due to several factors, including that infected eczema is not that common in children, eligible patients did not consult very frequently and the clinicians reported there was a lack of a standard, clear definition of infected eczema. However, of greater concern is that some children with ‘clear infection’ were not recruited to the study because either the clinician or parent was unhappy about them being in a trial that risked them receiving no antibiotic treatment. Despite this, more than 90% of the included participants did have ‘classical’ signs of infection (weeping, crusting, pustules or painful skin). However, the study specifically excluded children who had clinically severe infections, children who used oral or topical antibiotics to treat a skin infection within the past week and those who used potent or very potent topical corticosteroids within the past 2 days. On top of these exclusions, there was still a strong feeling among clinicians and parents that there were some clinical presentations that should be treated with antibiotics, or at least that the risks of no treatment were too great to include them in the trial. In addition, objective assessments suggested that only just over 20% and 16% of children had weeping and pustules respectively. Over two-thirds of the children were recruited from 1 centre. This might affect the generalisability of the results to other settings.

One possible explanation for the lack of efficacy seen with topical antibiotics might be the fact that almost a third of children from whom *S. aureus* was cultured had organisms that were resistant to fusidic acid. For oral antibiotics, low levels of adherence might have contributed to the lack of efficacy (only 42.4% of children in the oral flucloxacillin arm took 80% or more of their recommended doses). However, such low adherence is likely to reflect clinical practice. Oral flucloxacillin preparations are often considered by children to be unpalatable.

In conclusion, this RCT is currently the best published evidence available on the effectiveness of oral and topical antibiotics in children with infected eczema. Even so, interpretation is restricted by the
relatively small numbers of children included and several important limitations, most notably clinicians’ and parents’ exclusion of children with infections that they felt should be treated by antibiotics, as well as the planned exclusion by the investigators of other children with more severe infections. The results suggest that oral or topical antibiotics may not benefit children who have mild infections of eczema, but this needs to be interpreted with caution for children with more severe infections. The NICE guideline on *atopic eczema in under 12s* restricts use of oral or topical antibiotics in children with infected eczema to no more than 2 weeks.

**Study sponsorship**

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**References**

2. Schram ME, Spuls PI, Leeflang MMG et al. (2012) *EASI (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference* Allergy; 67: 99–106

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