Supplementary materials for:

Francis NA, Ridd MJ, Thomas-Jones E, et al. Oral and topical antibiotics for clinically infected eczema in children: a pragmatic randomized controlled trial in ambulatory care. *Ann Fam Med*. 2017;15(2):124-130.

# Appendix 1

## Inclusion criteria

Children (aged 3 months to less than eight years) with atopic eczema (as defined by UK working party) who presented with **clinically suspected infected eczema**. This could include children where:

- The eczema was failing to respond to standard treatment with emollients and / or mild to moderate topical corticosteroids.
- There was a flare in the severity or extent of the eczema.
- There was weeping or crusting.

## Exclusion criteria

Children were not eligible for inclusion if they had:

- Used oral or topical antibiotics to treat a skin infection within the past week.
- Used potent or very potent topical corticosteroids within the past two days [Time frame for topical corticosteroid use and use of oral steroids in the past week as an exclusion criteria were changed during the study].[1]
- Features suggestive of eczema herpeticum (significant pain, punched out lesions).
- Known significant comorbid illness (e.g. significant immune compromise)[Exclusions for renal or hepatic impairment, and significant congenital or acquired immunosuppression, were combined to form the criteria listed above during rercruitment].[1]
- Allergy to fusidic acid or both penicillin and erythromycin.
- Contraindication to any study medication (penicillin, erythromycin, fusidic acid).
- A treating clinician that believed the patient had a severe infection requiring immediate antibiotics or was arranging immediate hospitalisation or urgent (same or next day) dermatology referral because of the severity of the eczema or suspected infection.

Or if:

- A parent/ legal guardian was unable to provide written informed consent.
- A parent/legal guardian (or a person delegated by the parent/legal guardian) was not available for follow-up visits and who did not understand English well enough to complete verbal and written questionnaires.

[1] Changes to the exclusion criteria were made in December 2013, 6 months after recruitment started. 50 Participants had been recruited before the changes were introduced, and 18 had been assessed as ineligible. None of the ineligible patients would have been eligible with the new criteria.

**Appendix 2 – Microbiology processing**

Swabs were analysed for presence of S. *aureus* and β-haemolytic *Streptococci* (including Group A Streptococcus). Both nasal and eczema wound swabs were cultured onto non-selective media (Columbia blood agar (CBA), Oxoid, UK), *S. aureus* selective media (mannitol salt agar (MSA), Oxoid, UK) and Streptococcus selective media (Columbia with nalidixic acid and colistin (CNA), Oxoid, UK). Each swab was streaked to determine a semi-quantitative count (-+, +, ++, +++). Oropharyngeal (oral) swabs were cultured using a spiral plater (WASP, Don Whitley, UK) to achieve accurate counts of *S. aureus* or B-haemolytic streptococci onto CBA, MSA, CNA plus CNA + 1mg/L oxacillin, CNA + 1mg/L erythromycin, CNA + 1mg/L fusidic acid and CNA + 16mg/L fusidic acid. The antimicrobial media was used to detect any penicillin resistant streptococci, methicillin resistant *S. aureus* (MRSA), fusidic acid resistant *S. aureus* and erythromycin resistant *S. aureus* or streptococci.

The identity of all isolates were confirmed using the Matrix Assisted Laser Desorption Ionisation – Time of Flight (MALDI-ToF) instrument and Streptococcal groups confirmed using a latex agglutination Strep grouping kit (Pro-lab, UK). For all *S. aureus* & streptococcal isolates, susceptibilities to oxacillin, erythromycin, clindamycin, fusidic acid, cefoxitin, tetracycline were determined by EUCAST disc testing.

**Appendix 3 – Missing data / data cleaning rules**

**POEM**

Rules for dealing with the POEM score were obtained from the Centre for Evidence Based Dermatology (http://www.nottingham.ac.uk/research/groups/cebd/resources/index.aspx):

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28
- If two or more questions are left unanswered the questionnaire is not scored
- If two or more response options are ticked, the response option with the highest score should be recorded
- If there is a response between two tick boxes, the lower of the two score options should be recorded

**EASI**

If missing exists in any item then the total score was recorded as missing.

**Other scores (DFI, IDQoL/CDLQI)**

If less than half of items were missing, we used the averaged scores to populate the whole scores. If half the items or more were missing, we recorded the total scores as missing.

# Appendix 4 – Trial protocol

**THE CREAM STUDY – CHILDREN WITH ECZEMA, ANTIBIOTIC MANAGEMENT STUDY.**

Version 2.2 08/01/2015

| | |
|---|---|
| **Sponsor:** | Cardiff University, 7th Floor, 30-36 Newport Road, Cardiff, CF24 ODE |
| **Sponsor ref:** | SPON 846-10 |
| **Funder:** | National Institute for Health Research, Health Technology Assessment (NIHR HTA) |
| **Funder ref:** | 09/118/03 |
| **REC ref:** | 12/WA/0180 |
| **EudraCT ref:** | 2011-003591-37 |

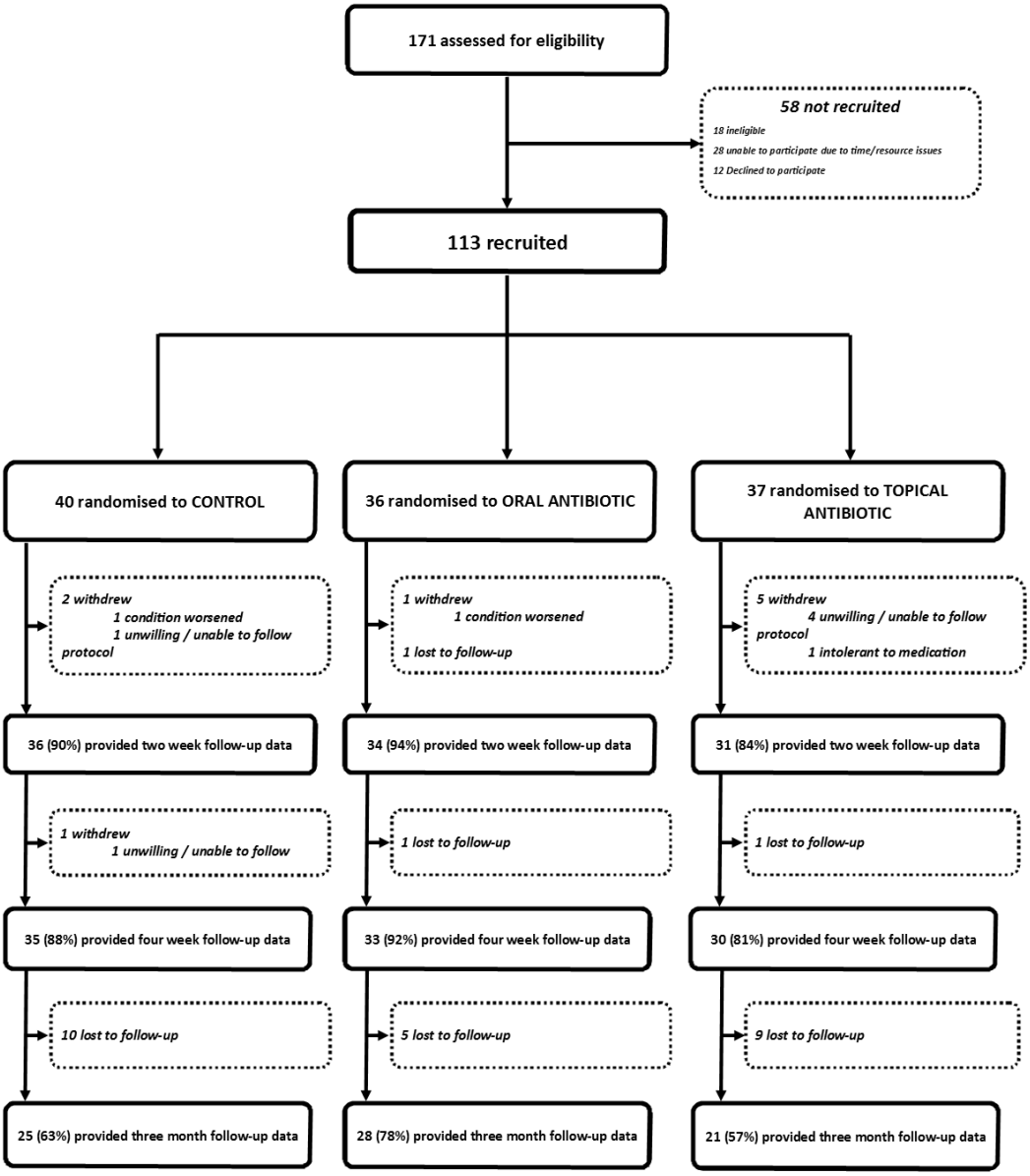
ISRCTN96705420; UKCRN ID: 11233

**This protocol has been authorised by:**

| | | | |
|---|---|---|---|
| Dr M Robling<br>**Name** | SEWTU Director<br>**Role** | **Signature** | **08/01/2015**<br>**Date** |
| Dr N Francis<br>**Name** | Chief Investigator<br>**Role** | **Signature** | **08/01/2015**<br>**Date** |
| Professor F Sullivan<br>**Name** | Chief Investigator<br>**Role** | **Signature** | **08/01/2015**<br>**Date** |

# Appendix 5

## Consort Flow Diagram



**Appendix 6 – Effect of oral and topical antibiotics on family impact and quality of life**

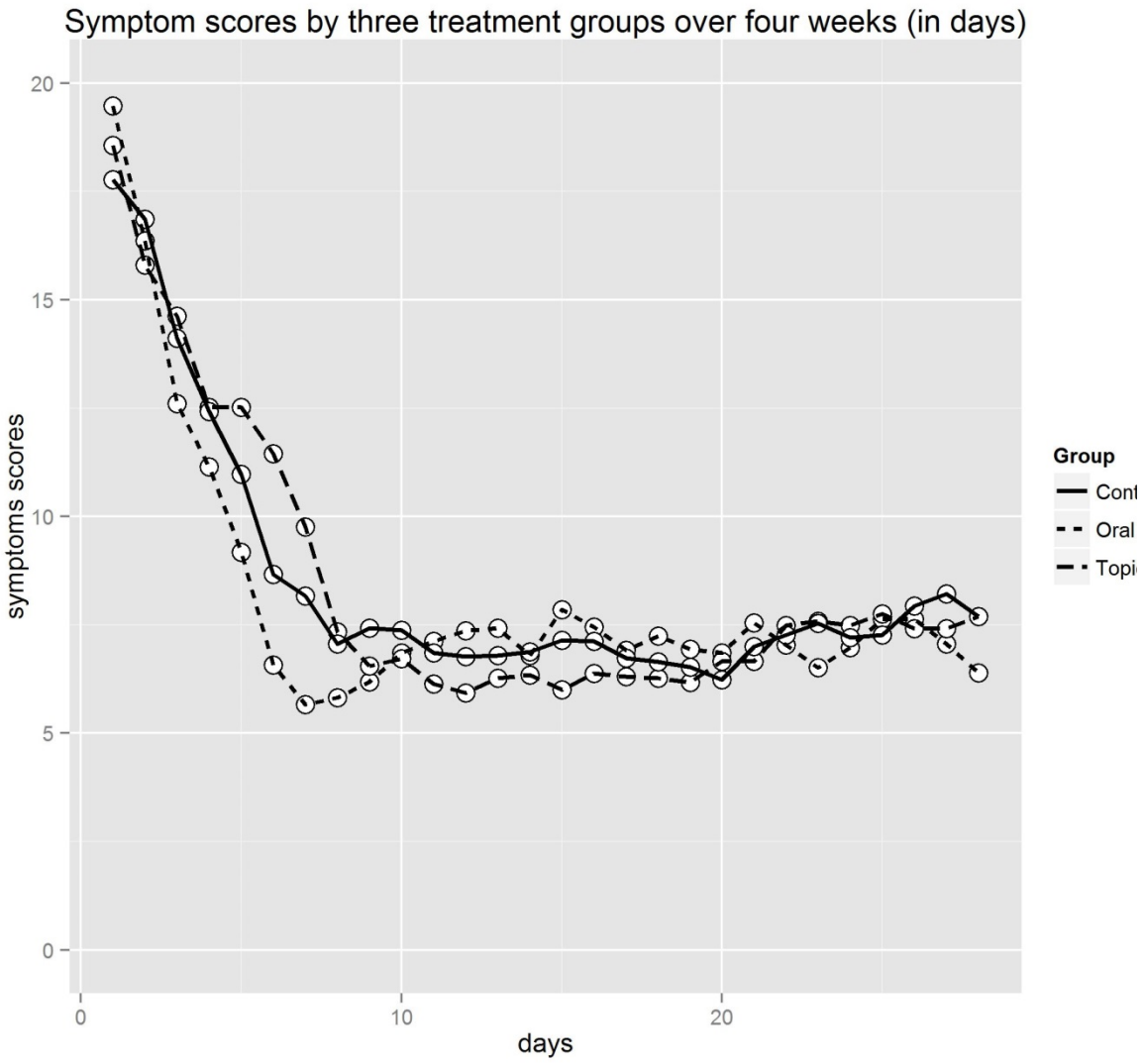
| Outcome | Control | | | Oral antibiotic | | | | Topical antibiotic | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Baseline – mean (SD) | Follow-up – mean (SD) | N | Baseline – mean (SD) | Follow-up – mean (SD) | Intervention effect (95% CI) | N | Baseline – mean (SD) | Follow-up – mean (SD) | Intervention effect (95% CI) |
| **DFI**[1] | 3 | | | | | | | | | | |
| **- 2 weeks** | 5 | 5.3 (4.7) | 2.6 (4.8) | 34 | 6.5 (5.2) | 3.7 (4.4) | 0.2 (-0.2, 0.5) | 31 | 8.2 (5.7) | 4.8 (5.4) | 0.2 (-0.2, 0.6) |
| **- 4 weeks** | 3 | | | | | | | | | | |
| | 5 | 5.3 (4.7) | 3.1 (4.9) | 33 | 6.5 (5.3) | 3.5 (4.6) | -0.0 (-0.4, 0.4) | 30 | 7.8 (5.5) | 4.2 (4.8) | -0.0 (-0.4, 0.4) |
| **- 3 months** | 2 | | | | | | | | | | |
| | 4 | 6.1 (4.8) | 3.5 (4.3) | 25 | 6.7 (5.5) | 3.5 (4.4) | -0.0 (-0.6, 0.5) | 20 | 6.6 (4.9) | 4.1 (5.5) | -0.0 (-0.6, 0.6) |
| **IDQoL**[2] | 2 | | | | | | | | | | |
| **- 2 weeks** | 0 | 9.5 (2.6) | 6.1 (3.7) | 25 | 10.0 (3.8) | 6.7 (3.3) | 0.1 (-0.1, 0.3) | 22 | 10.0 (4.1) | 7.2 (3.0) | 0.2 (-0.0, 0.4) |
| **- 4 weeks** | 2 | | | | | | | | | | |
| | 0 | 9.5 (2.6) | 6.9 (3.7) | 24 | 10.1 (3.9) | 6.6 (3.2) | -0.0 (-0.3, 0.2) | 22 | 10.0 (4.1) | 7.1 (3.0) | 0.1 (-0.2, 0.3) |
| **- 3 months** | 1 | | | | | | | | | | |
| | 6 | 9.6 (2.6) | 7.3 (2.6) | 18 | 10.5 (4.0) | 6.0 (3.2) | -0.2 (-0.4, 0.0) | 15 | 9.5 (3.9) | 6.7 (3.5) | -0.1 (-0.3, 0.2) |
| **CDLQI**[3] | 1 | | | | | | | | | | |
| **- 2 weeks** | 4 | 7.6 (6.0) | 1.8 (2.0) | 9 | 9.8 (4.4) | 4.1 (3.0) | 0.4 (-0.2, 1.0) | 9 | 9.6 (6.4) | 5.9 (6.3) | 0.7 (0.1, 1.3) |
| **- 4 weeks** | 1 | | | | | | | | | | |
| | 4 | 7.6 (6.0) | 4.6 (5.9) | 9 | 9.8 (4.4) | 4.4 (4.8) | -0.2 (-0.8, 0.5) | 8 | 8.0 (4.2) | 3.0 (2.2) | -0.2 (-0.9, 0.5) |
| **- 3 months** | 8 | 8.9 (7.1) | 6.2 (6.4) | 6 | 8.2 (4.3) | 5.6 (6.7) | -0.1 (-1.0, 0.7) | 6 | 6.5 (3.4) | 4.6 (4.6) | -0.1 (-1.0, 0.7) |

[1] Dermatitis Family Index

[2] Infants Dermatitis Quality of Life

[3] Children's Dermatology Life Quality Index

**Appendix 7**



**Appendix 8 – Adherence to medication and CACE analysis**

97 (86%) participants provided data on use of study medication. Overall mean adherence to oral antibiotic (or matched placebo) was 61.3%. Adherence in the oral antibiotic group was slightly higher than in the other arms (55.1%, 70.4%, 58.3% in CTRL, OA and TA arms respectively) although the differences were not significant. The overall mean adherence to topical antibiotic (or matched placebo) was 81.8%, and there was no significant difference by treatment group (80.4%, 84.1%, 80.8% in control, oral antibiotic and topical antibiotic respectively).

**Mean weight of remaining study medication by study group and overall**

| | Study Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Control | | Oral Antibiotic | | Topical Antibiotic | | Overall | |
| | n | mean (SD) | n | mean (SD) | n | mean (SD) | n | mean (SD) |
| Flucloxacillin or placebo weight (g) | 36 | 312 (191) | 30 | 243 (102) | 25 | 260 (110) | 91 | 275 (147) |
| Erythromycin or placebo weight (g) | 1 | 126 (NA) | 0 | NA (NA) | 2 | 160 (4) | 3 | 149 (20) |
| Fusidic acid or placebo weight (g) | 37 | 37 (20) | 30 | 36 (21) | 27 | 34 (20) | 94 | 36 (20) |

Adjusting for adherence using CACE analyses, and analysis of the primary outcome using multiple imputation, did not result in meaningful changes to the results.

## Appendix 9 – Growth of *S. aureus* from skin swabs and resistance to study antibiotics in *S. aureus* from baseline skin swabs

| | Control | | | Oral Antibiotic | | | Topical Antibiotic | | | Overall | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Culture positive - % of participants (95% CI) | Difference from baseline | N | Culture positive - % of participants (95% CI) | Difference from baseline | N | Culture positive - % of participants (95% CI) | Difference from baseline | N | Culture positive - % of participants (95% CI) | Difference from baseline |
| **Baseline** | 40 | 60.0 (44.1, 75.9) | - | 36 | 83.3 (70.5, 96.1) | - | 36 | 66.7 (50.5, 82.8) | - | 112 | 69.6 (61.0,78.3) | - |
| **2 weeks** | 34 | 44.4 (34.5,54.4) | -15.9 (-39.1, 7.4) | 34 | 52.9 (35.3, 70.6) | -30.4 (-51.6, -9.2) | 31 | 35.5 (17.6, 53.3) | -31.2 (-54.8, -7.6) | 99 | 44.4 (34.5,54.4) | -25.2 (-38. -12.1) |
| **3 months** | 25 | 40.0 (19.4, 60.6) | -20.0 (-45.4, 5.4) | 26 | 30.8 (11.8, 49.8) | -52.6 (-74.1, -31.0) | 21 | 38.1 (15.4, 60.7) | -28.6 (-55.3, -1.9) | 72 | 36.1 (24.7, 47.5) | -33.5 (-47. -19.5) |

**Resistance in *S. aureus* from skin at baseline – n (%)**

| | N | FLU[a] | ERY[b] | FA[c] | N | FLU[a] | ERY[b] | FA[c] | N | FLU[a] | ERY[b] | FA[c] | N | FLU[a] | ERY[b] | FA[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline** | 24 | 0 (0.0) | 2 (8.3) | 6 (25.0) | 30 | 1 (3.3)) | 5 (16.7) | 7 (23.3) | 24 | 1 (4.2) | 2 (8.3) | 8 (33.3) | 78 | 2 (2.6) | 9 (11.5) | 21 (26.9 |
| **2 weeks** | 16 | 0 (0.0) | 2 (12.5) | 5 (31.2) | 18 | 0 (0.0) | 1 (5.6) | 1 (5.6) | 11 | 2 (18.2) | 0 (0.0) | 8 (72.7) | 45 | 2 (4.4) | 3 (6.7) | 14 (31.1 |
| **3 months** | 10 | 0 (0.0) | 1 (10.0) | 2 (20.0) | 8 | 1 (12.5) | 1 (12.5) | 0 (0.0) | 8 | 1 (12.5) | 1 (12.5) | 2 (25.0) | 26 | 2 (7.7) | 3 (11.5) | 4 (15.4 |

*a) No. (%) resistant to flucloxacillin; b) No. (%) resistant to erythromycin; c) No. (%) resistant to fusidic acid*

**Appendix 10 – Adverse effects**

| | Control (N=35) | | Oral antibiotic (N = 33) | | Topical antibiotic (N = 29) | | Overall (N = 97) | |
|---|---|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Nausea | 3 | 8.6 | 2 | 6.1 | 1 | 3.4 | 6 | 5.3 |
| Vomiting | 6 | 17.1 | 4 | 12.1 | 2 | 6.9 | 12 | 12.4 |
| Diarrhoea | 5 | 14.3 | 5 | 15.2 | 5 | 17.2 | 15 | 15.5 |
| Tummy pain | 2 | 5.7 | 3 | 9.1 | 3 | 10.3 | 8 | 8.2 |
| Joint pains | 0 | 0.0 | 1 | 3.0 | 2 | 6.9 | 3 | 3.1 |
| New rash | 8 | 22.9 | 4 | 12.1 | 5 | 17.2 | 17 | 17.5 |
| No. patients with 1 or more adverse effect | 13 | 37.1 | 10 | 30.3 | 11 | 37.9 | 34 | 35.1 |