NICE National Institute for Health and Care Excellence

Surveillance report 2016 – Atopic eczema in under 12s: diagnosis and management (2007) NICE guideline CG57

Surveillance report

Published: 21 July 2016

www.nice.org.uk

Contents

Surveillance decision

We will not update the guideline at this time.

Reason for the decision

We found 52 new studies through surveillance of this guideline: 24 in a search of systematic reviews and randomised controlled trials (between October 2013 and November 2015) and 27 identified by topic experts. A further study was identified through post-publication communications. None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations. These studies included new evidence on:

- Assessment of severity
- Epidemiology
- Management of trigger factors
- Treatment
- Education and adherence to therapy

None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations.

We did not find any new evidence on:

- Diagnosis
- Psychological and psychosocial wellbeing and quality of life
- Identification of trigger factors
- Indications for referral

We found new evidence related to the research recommendations on methods to measure severity of atopic eczema, house dust mite avoidance strategies, optimal feeding regimen in the first year of life, effects of improving the control of atopic eczema in the first year of

life, treatment, and education and adherence to therapy. This new evidence was not considered to fully address these research recommendations or affect current recommendations. We did not find new evidence that would affect other research recommendations.

The majority of topic experts considered the guideline still relevant to clinical practice. One topic expert felt that there is a comprehensive body of new evidence to inform an update of the guideline. Topic experts highlighted that a topical corticosteroid (Elocon: mometasone furoate) is generic now and therefore cheaper. For topical corticosteroids, the current guideline already recommends the drug with the lowest acquisition cost taking into account potency tailoring to the severity of the child's atopic eczema, pack size and frequency of application. Topic experts also highlighted that children should be referred for allergy tests recognising that referral for allergy tests could have a cost impact. However, the current guideline does not recommend having allergy tests for most children (recommendation 1.4.1.5: 'Healthcare professionals should reassure children with mild atopic eczema and their parents or carers that most children with mild atopic eczema do not need to have tests for allergies'). Therefore, it was felt that an update of the guideline related to allergy tests and topical corticosteroids is not necessary at this time. Topic experts also mentioned the need to review the food allergy section of the guideline, particularly around allergy testing. They also felt there would be value in giving greater clarity about safety of pimecrolimus and tacrolimus in children. However, all these areas are already covered in other NICE guidance on food allergy in under 19s: assessment and diagnosis (2011) NICE guideline CG116 and tacrolimus and pimecrolimus for atopic eczema (2004) NICE technology appraisal guidance 84. Other areas for consideration highlighted by topic experts included prevention of eczema and the inclusion of adults. However, prevention of eczema and diagnosis and management for adults are out of scope of this guideline and outside the original remit from the Department of Health.

Equalities

Finally, topic experts also highlighted some inequalities in access to specialist allergy services around the UK and that children from South Asian communities get less good care and more severe disease. However, no evidence was identified in relation to this issue from our searches and our recommendations do not exclude these groups.

Overall decision

After considering all the new evidence and views of topic experts, we decided not to

update this guideline.

See how we made the decision for further information.

Commentary on selected new evidence

With advice from topic experts we selected 3 studies for further commentary.

Treatment – Topical corticosteroids; Topical calcineurin inhibitors

We selected the randomised open-label study by Sigurgeirsson et al. (2015) for a full commentary because this study offers safety data on pimecrolimus (a topical calcineurin inhibitor) and topical corticosteroids.

What the guideline recommends

NICE guideline CG57 recommends that health professionals should discuss the benefits and harms of treatment with topical corticosteroids with children with atopic eczema and their parents or carers, emphasising that the benefits outweigh possible harms when they are applied correctly. It is recommended that topical corticosteroids for atopic eczema should be prescribed for application only once or twice daily (this recommendation is from frequency of application of topical corticosteroids for atopic eczema (2004) NICE technology appraisal guidance 81). NICE guideline CG57 also recommends that potent topical corticosteroids should not be used in children aged under 12 months without specialist dermatological supervision.

NICE guideline CG57 recommends pimecrolimus, within its licensed indications, as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged 2–16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy (this recommendation is from tacrolimus and pimecrolimus for atopic eczema (2004) NICE technology appraisal guidance 82).

Methods

Sigurgeirsson et al. (2015) conducted a multicentre randomised open-label parallel group study in Argentina, Belgium, Canada, Chile, China, Colombia, Czech Republic, Ecuador, Germany, Greece, Guatemala, Hungary, Iceland, Japan, Netherlands, Peru, Poland,

Portugal, Russia, South Africa, Spain, Sweden, Taiwan, Turkey, United Kingdom United States, and Venezuela. Eligible infants (aged ≥3 to 12 months) had a diagnosis of atopic dermatitis with disease affecting ≥5% of the total body surface area and mild-to-moderate atopic dermatitis (AD). The study excluded children if they were treated with systemic corticosteroids, cytostatic drugs, or phototherapy (within 4 weeks of the first application of study medication); with topical tacrolimus ointment or pimecrolimus (within 2 weeks); with topical therapy including topical corticosteroids (within 3 days); or if children were immunocompromised, or those with a history of malignant disease, active acute viral skin infection, or clinically infected AD. The study randomised 1,205 infants to pimecrolimus 1% cream (PIM) and 1,213 infants to topical corticosteroids (TCS). PIM was used twice daily until complete AD clearance and TCS were used according to label. During exacerbation (flare, unacceptable severity of itching), PIM had to be stopped and TCS used. The study included a table with the complete treatment scheme including treatment for dry skin and infection (Supplemental Table 4).

Primary outcome measures were safety (assessed by adverse events), growth rate and immunology assessments. Secondary outcome measures were Investigator's Global Assessment (IGA) and the total body surface area (TBSA) involved with AD.

Results

The frequency of adverse events (AEs) was similar in both treatment groups (any AE: PIM 96.4% and TCS 95.6%). The top 5 most common AEs were nasopharyngitis, pyrexia, bronchitis, otitis media, and diarrhoea.

The study reported that there was no difference in growth rate (as measured by height and weight at each visit) between PIM and TCS groups without presenting any data.

The effects of PIM and TCSs on the developing immune system were reported for three immunology assessments:

- Positive antibody titers were reported for 5 vaccines (p values were not reported):
  - Tetanus: PIM (91.1%) and TCS (88.9%) (OR 1.3, 95% CI 0.6 to 2.5)
  - Hepatitis B: PIM (34.6%) and TCS (38.2%) (OR 0.9, 95% CI 0.6 to 1.3)
  - Measles: PIM (98.9%) and TCS (96.3%) (OR 3.5, 95% CI 0.7 to 17.0)
  - Varicella: PIM (87.1%) and TCS (84.1%) (OR 1.3, 95% CI 0.3 to 4.8)
  - Haemophilus influenza type b: PIM (96.3%) and TCS (96.8%) (OR 0.9, 95% CI 0.1 to 14.6).
- Immunoglobulin (Ig) levels, peripheral blood T and B lymphocytes were similar in both PIM and TCS groups and considered normal.
- The proportion of infants with positive candida skin tests (measuring cellular immune response) was similar for both groups. T-cell function (measuring immune response) was similar for both PIM and TCS groups.

Efficacy was reported at 3 weeks and 5 years:

- Overall IGA treatment success: 3 weeks (PIM 52.6%, TCS 50.5%), 5 years (PIM 88.7%, TCS 92.3%)
- Face IGA treatment success: 3 weeks (PIM 61.0%, TCS 61.8%), 5 years (PIM 96.6%, TCS 97.2%)
- TBSA affected decreased from 16% at baseline: 3 weeks (PIM 3.8%, TCS 4.0%), after 1.5 years (0%).

These data were reported with percentages without any statistical analyses.

Strengths and limitations

Strengths

Strengths of this study were that it reported a long-term follow-up (5 years), it reported the randomisation process, missing outcome data were similar across intervention groups and it was a multicentre study.

Limitations

Limitations of the study were:

- The outcome is likely to be influenced by the lack of blinding because PIM is supposed to be used as second-line treatment and TCS as first-line treatment. Participants are likely to know this information.
- Efficacy was evaluated by investigators. It is unclear whether investigators also assessed AEs and growth rate.
- The study population (infants aged ≥3 to 12 months) only partially matches the population looked at in NICE guideline CG57 (children from birth up to the age of 12 years) which limits the applicability of the results. PIM is only licensed for use in children over the age of 2 years.
- Immunology assessments were done in a proportion of participants without an explanation of why (PIM 383/1205 and TCS 391/1213).
- There were some infants with severe and very severe facial eczema at baseline and a potential imbalance regarding severe facial eczema between the PIM and TCS groups. This imbalance was not statistically analysed, controlled in the analysis or discussed in the article.
- Three more secondary outcomes were listed in the registered protocol but not reported in this publication: quality of life, blood pressure and pulse.
- A topic expert mentioned that skin atrophy (skin thinning) is an important outcome for this study but this was not reported as an outcome. The topic expert highlighted that skin atrophy data was later reported in the comments section of the Journal of Pediatrics (skin atrophy: PIM (0 participants) and TCS (1 participant, 0.1%)). The authors clarified that 'skin atrophy was not specifically measured in our study using techniques such as ultrasound, dermoscopy or histology'.

Impact on guideline

The new evidence suggests that PIM and TCS may be as safe for long-term management of mild to moderate atopic dermatitis in children as TCS alone. These data support NICE guideline CG57 which already recommends topical corticosteroids emphasising that the benefits outweigh possible harms when they are applied correctly and recommends

pimecrolimus, within its licensed indications, as an option for second-line treatment. In this study, pimecrolimus was used outside its licensed indications which states it should not be used in children under 2 years. Recommendations for PIM and TCS have been taken from tacrolimus and pimecrolimus for atopic eczema (2004) NICE technology appraisal guidance 82 and frequency of application of topical corticosteroids for atopic eczema (2004) NICE technology appraisal guidance 81.

Treatment - Complementary therapies

We selected the randomised controlled trial (RCT) by Wang and Wang (2015) for a full commentary because it considered the role of probiotics for the treatment of atopic dermatitis and this was an area where limited evidence was identified during guideline development.

What the guideline recommends

During guideline development, the Guideline Committee did not find good evidence to support the use of probiotics in the management of atopic eczema in children. NICE guideline CG57 recommends that children with atopic eczema and their parents or carers should be informed that the effectiveness and safety of complementary therapies such as homeopathy, herbal medicine, massage and food supplements for the management of atopic eczema have not yet been adequately assessed in clinical studies.

Methods

Wang and Wang (2015) conducted a randomised placebo-controlled study of *Lactobacillus paracasei* (LP), *Lactobacillus fermentum* (LF), and their mixture (LP + LF mixture) compared with placebo in children aged 1-18 years with moderate to severe atopic dermatitis. The study randomised 165 children to receive probiotics (55 per group: LP, LF and LP + LF mixture) and 55 children to placebo. Probiotics and placebo were provided as capsules which were taken once a day for 3 months.

Primary outcomes were changes in the following after 3 months of intervention compared to baseline:

- severity of atopic dermatitis (measured with the Scoring Atopic Dermatitis Index [SCORAD])

- quality of life (measured with the Family Dermatology Life Quality Index (FDLQI) and the Children's Dermatology Life Quality Index (CDLQI)).

Secondary outcomes, which were also assessed at baseline and after 3 months, were:

- changes in total serum immunoglobulin (IgE)
- skin prick test reactivity
- serum and urine biomarkers
- faecal probiotic species composition.

Results

The severity of atopic eczema was statistically significantly reduced after treatment in each group shown by lower SCORAD scores:

- LP (baseline: mean 50.93, standard deviation (SD) 19.42, month 3: mean 25.62, SD 22.35, $p<0.05$, n=55)
- LF (baseline: mean 52.25, SD 16.85, month 3: mean 28.38, SD 20.43, $p<0.05$, n=53)
- LP + LF (baseline: mean 51.90, SD 18.90, month 3: mean 24.17, SD 17.63, $p<0.05$, n=51)
- Placebo (baseline: mean 54.08, SD 17.06, month 3: mean 39.39, SD 18.34, $p<0.05$, n=53)
- The mean SCORAD score was significantly different for the 4 groups at month 3 ($p<0.001$).

Modelling adjusting for age, sex, and topical steroid use showed that the intervention groups had significantly lower SCORAD scores than the placebo group after five visits (these data were reported in the supplementary information):

- LP (β -9.53, 95% confidence interval [CI] -15.98 to -3.08, $p<0.05$)
- LF (β -7.67, 95% CI -14.21 to -1.13, $p<0.05$)
- LP + LF (β -9.86, 95% CI -16.44 to -3.28, $p <0.05$; overall $p=0.009$).

Subgroup analysis showed that SCORAD scores significantly reduced after probiotics

treatment (the three probiotics groups combined) in children <12 years old (n=178) from baseline to 3 months (probiotics groups mean change -0.55 [SD 0.31], placebo mean change -0.22 [SD 0.27], p<0.001). Although the mean change in SCORAD scores was significant, it is unclear if this effect size is of clinical importance.

Family quality of life was significantly improved after treatment in the three intervention groups shown by lower FDLQI scores:

- LP (baseline: mean 10.71, SD 6.17, month 3: mean 8.29, SD 6.84, p<0.05, n=55)
- LF (baseline: mean 12.45, SD 6.57, month 3: mean 7.55, SD 6.71, p<0.05, n=53)
- LP + LF (baseline: mean 12.41, SD 5.50, month 3: mean 5.20, SD 4.07, p<0.05, n=51)
- Placebo (baseline: mean 10.17, SD 7.50, month 3: mean 8.79, SD 6.22, no p value reported, n=53)
- The mean FDLQI score was significantly different for the 4 groups at month 3 (p=0.02).

Modelling adjusting for age, sex, and topical steroid use showed no significant differences between intervention groups and placebo regarding FDLQI scores after five visits (this data was reported in the supplementary information):

- LP (β -0.17, 95% CI -2.18 to 1.85)
- LF (β -0.35, 95% CI -2.40 to 1.70)
- LP + LF (β -0.93, 95% CI -2.98 to 1.13, overall p=0.829).

Children's quality of life was significantly improved after treatment in the three intervention groups shown by lower CDLQI scores:

- LP (baseline: mean 11.38, SD 5.20, month 3: mean 7.20, SD 5.99, p<0.05, n=55)
- LF (baseline: mean 12.23, SD 6.92, month 3: mean 7.45, SD 6.74, p<0.05, n=53)
- LP + LF (baseline: mean 12.69, SD 6.11 month 3: mean 5.43, SD 4.10, p<0.05, n=51)
- Placebo (baseline: mean 10.98, SD 7.42, month 3: mean 8.98, SD 6.25, no p value reported, n=53)

- The mean CDLQI score was significantly different for the 4 groups at month 3 (p=0.03).

Modelling adjusting for age, sex, and topical steroid use showed no significant differences between intervention groups and placebo regarding CDLQI scores after five visits (this data was reported in the supplementary information):

- LP (β -0.55, 95% CI -2.52 to 1.42)
- LF (β -0.09, 95% CI -2.05 to 1.87)
- LP + LF (β -0.59, 95% CI -2.52 to 1.34, overall p=0.902).

Total serum IgE was significantly reduced in the LP and LP + LF groups but not in the LF and placebo groups. At the end of treatment, no significant difference was observed between the 4 groups:

- LP (baseline: mean 1055.11, SD 1219.50, month 3: mean 868.04, SD 1107.16, p<0.05, n=55)
- LF (baseline: mean 923.41, SD 1101.44, month 3: mean 799.76, SD 1051.19, p<0.05, n=53)
- LP + LF (baseline: mean 1228.78, SD 1524.66, month 3: mean 927.51, SD 1185.62, p<0.05, n=51)
- Placebo (baseline: mean 1443.24, SD 1548.75, month 3: mean 1234.78, SD 1237.38, no p value reported, n=53)
- The mean IgE level was not significantly different for the 4 groups at month 3 (p=0.27).

Skin prick test reactivity was significantly higher at month 3 in the placebo groups for mite, milk and egg sensitisation. For serum biomarkers, there were significant differences for interleukin (IL-4) (ng/mL) between the four groups with placebo showing the highest levels at month 3. The rest of the serum biomarkers (interferon gamma [IFN-γ], tumour necrosis factor alpha [TNF-α], and transforming growth factor beta [TGF-β]) did not show significant differences between the four groups. However, LF group looked like the levels dropped significantly compared to baseline. The urine biomarker eosinophilic protein X did not differ significantly between the four groups. For the faecal cell count, the placebo group showed the lowest faecal colony counts of *Bifidobacterium* and the highest faecal

colony counts of *Clostridium* compared to the three probiotic groups at month 3 and this difference was statistically significant.

Probiotics were expected to treat the allergy component of participants' atopic dermatitis. These results showed that just some of the biomarkers and sensitisations were improved in the probiotics groups. Therefore, this evidence is not strong regarding the immunological effect of probiotics on atopic dermatitis.

Strengths and limitations

Strengths

The strength of this study was the design: double-blind RCT. This means that probiotics effect was not confounded by unmeasured variables or by participants or investigators' expectations of probiotics effect.

Limitations

Limitations of the study were:

- The study population (children aged 1 to 18 years) only partially matches the population included in NICE guideline CG57 (children from birth up to the age of 12 years). Although a subgroup analysis was reported for children under 12 years old, this subgroup analysis was not listed in the trial registration.
- Small sample size (n=220 participants, 55 per group).
- Dermatitis Family Impact Questionnaire was listed in the trial registration but changed to Family Dermatology Life Quality Index in the publication.
- Decreased oral antihistamine use was listed in the registered protocol but not reported in the publication.
- There was inconsistency between the SCORAD scores and quality of life (FDLQI and CDLQI) results after adjusting for age, sex, and topical steroid use. This means that probiotics treatment improved the severity of atopic dermatitis with no improvements in quality of life. However, this inconsistency was not clarified or discussed.

Impact on guideline

The new evidence suggests that probiotics may be associated with reduction of atopic eczema severity in children but no change in quality of life. However, a systematic review by Boyle et al. (2008) concluded that evidence from 12 RCTs in children with eczema (n=781 participants) suggested probiotics were not effective for the treatment of eczema. Furthermore, the new evidence comes from a small RCT with limitations and inconsistent results meaning it is difficult to accurately conclude the impact of probiotics in the treatment of atopic eczema in children under 12 years. It would be premature to consider updating the guideline at this time. NICE guideline CG57 recommends that children with atopic eczema and their parents or carers should be informed that the effectiveness and safety of complementary therapies such as homeopathy, herbal medicine, massage and food supplements for the management of atopic eczema have not yet been adequately assessed in clinical studies.

Treatment

We selected the systematic review by Nankervis et al. (2016) for a full commentary because this is an update of a previous version which was included during guideline development and which covers all treatments for atopic eczema included by NICE guideline CG57.

What the guideline recommends

NICE guideline CG57 recommends using a stepped approach for managing atopic eczema in children which involves tailoring the treatment step to the severity of the atopic eczema. Treatment options according to severity of the atopic eczema are:

- Mild atopic eczema (emollients and mild potency topical corticosteroids)
- Moderate atopic eczema (emollients, moderate potency topical corticosteroids, topical calcineurin inhibitors, and bandages)
- Severe atopic eczema (emollients, potent topical corticosteroids, topical calcineurin inhibitors, bandages, phototherapy, and systemic therapy)

Recommendations related to other treatments are also included such as antihistamines, treatment for infections, and complementary therapies.

Methods

Nankervis et al. (2016) conducted a systematic review of 287 RCTs of 92 different interventions for atopic eczema. The total number of participants included in the RCTs was not provided as a summary data. RCTs were included if they were prospective, if participants were randomised to 2 or more groups, and if they were about therapeutic interventions for atopic eczema. RCTs were excluded if they compared people with and without atopic eczema in relation to adverse events, if they only reported changes in blood tests or cellular mechanisms, and if they were focused on eczema prevention. Participants of any age were included if their eczema met published diagnostic criteria or if they had been diagnosed by a clinician. A list of terms were identified as 'definitely not having atopic eczema' and therefore excluded from the review (examples of such terms were seborrheic eczema, contact eczema and allergic contact eczema). Main outcome measures included:

- Changes in patient-rated symptoms of eczema
- Global severity rated by patients or their clinicians
    - Global changes in composite rating scales were used if the above outcomes were not available
- Quality of life
- Adverse events.

Secondary outcome measures included changes in individual signs of atopic eczema. There was no meta-analysis at all because the scope of the review was wide and it was considered that participants, interventions and outcomes were heterogeneous. Methodological quality was assessed using the Cochrane collaboration risk of bias assessment tool.

Results

Results were reported by type of intervention and comparison. For the purpose of this surveillance report, only results on RCTs including children were summarised, although age was not reported for all trials. This approach was taken to incorporate evidence relevant to the guideline scope of NICE guideline CG57 which covers children from birth up to the age of 12 years who have atopic eczema.

Topical corticosteroids

Topical corticosteroids were compared with placebo (14 RCTs, participant age not reported) or active treatments excluding topical immunomodulators (12 RCTs, 3 did not report age and 9 included children):

- Three trials reported significant improvement in the severity of eczema in the groups randomised to topical corticosteroids (0.05% fluticasone propionate or mometasone furoate) compared with active treatments (1% hydrocortisone, 0.1% hydrocortisone butyrate or methylprednisolone aceponate).
- Three trials reported no significant differences between the following comparisons:
  - Short bursts of potent topical corticosteroids and longer bursts of milder topical corticosteroids (aged 1 to 15 years, n=207);
  - 1% hydrocortisone combined with the antifungal agent miconazole and 1% hydrocortisone alone (aged 5 to 14 years, n=30);
  - 0.1% flucinonide cream once daily and 0.1% flucinonide cream twice daily (aged <18 years, n=126).
- Two trials reported no results for severity of atopic eczema:
  - 0.1% micronized desonide cream and 0.05% betamethasone dipropionate cream (aged ≤8 years, n=29);
  - 0.1% mometasone furoate cream and 0.05% desonide cream (aged 2 to 12 years, n=25).
- One trial (n=40 children with atopic eczema) reported that there was a significant improvement in eczema severity in children using 0.05% clobetasone butyrate ointment for 4 days a week compared with children using the treatment continuously.

Topical immunomodulators

Tacrolimus was compared with placebo in 12 trials with 3 studies on prevention of flare-ups reporting results for children:

- One trial reported that quality of life was comparable between treatments and that pruritus and impetigo was more frequent in the tacrolimus group compared with the placebo group.
- A trial including children and adults reported that tacrolimus significantly increased the number of flare-free treatment days and the time to first flare compared to placebo.
- A trial included children and adults (n=70) and reported that the cumulative itch recurrence was lower with tacrolimus compared to placebo which was an emollient.

Tacrolimus was compared with active treatments in 15 trials, 5 of which included children:

- Tacrolimus was compared with hydrocortisone in 2 trials with mixed results:
  - One trial reported greater reduction of eczema severity with tacrolimus compared to 1% hydrocortisone acetate whilst the second trial reported higher reduction of eczema severity with hydrocortisone butyrate compared to 0.03% tacrolimus and 0.1% tacrolimus.
- Tacrolimus was compared with other topical corticosteroids in 3 trials with no differences observed between treatments in clearing eczema.

Pimecrolimus was compared with placebo in 17 trials, 3 of which reported results in children:

- Two trials reported that the number of participants without flares over 6 months of treatment was significantly lower with pimecrolimus compared to placebo. One of the trials reported that severity of eczema was in favour of pimecrolimus with a statistically significant difference.
- One trial reported that the proportion of infants and children not using topical corticosteroid treatment after 1 year was higher in the pimecrolimus group compared to the placebo group.

Pimecrolimus was compared with active treatments in 5 trials but no specific results for children were reported.

Tacrolimus was compared with pimecrolimus in 8 trials, with 7 including children or children and adults:

- Four trials compared either 0.1% or 0.03% tacrolimus with 1% pimecrolimus twice daily. Three RCTs reported that eczema severity was reduced significantly greater with tacrolimus compared to pimecrolimus and treatment success rate was also better with tacrolimus compared to pimecrolimus. Conversely, a trial including children (2 to 17 years) reported a statistically significant reduction in pruritus with pimecrolimus compared to tacrolimus.
- Three trials compared different regimens of tacrolimus or pimecrolimus in children but reported no differences in outcomes between frequency of daily applications.

One trial including children (n=376) compared a combination of 0.05% fluticasone propionate plus 1% pimecrolimus against 0.05% fluticasone propionate plus placebo and reported no differences between the groups.

Topical corticosteroids with occlusive therapy

Five trials evaluated the use of wet wrap bandages although 1 study was not included in this commentary because they did not conduct a comparison between the treatment groups on severity of eczema. All trials included children or children and adults. In 2 studies, the use of wet wraps in combination with medication improved eczema outcomes whilst one study reported that atopic dermatitis and quality of life improved significantly more without wet wraps. One study reported no differences in eczema outcomes with wet wraps.

Emollients and other topical treatments

Most of the 15 included trials compared emollients (often applied concurrently with topical corticosteroid treatment) against topical corticosteroids alone, other emollients, or no treatment. Seven trials reported results for children:

- Two trials evaluated exomega milk but did not report any differences between this intervention and a comparator group in severity of eczema (either no equivalent treatment or a cleaning bar).
- One trial reported significantly greater reductions in scaling, skin dryness scaling, redness, and participant-assessed itching with Axera (a liquid soap containing ammonium lactate and urea) compared to commercially available liquid soap.

- Sunflower oleodistillate emollient was compared against a topical corticosteroid in 2 trials. Both trials did not find significant differences between the groups regarding severity of eczema or quality of life.
- Emollients containing ceramide were evaluated in 2 trials. One trial compared ceramide-dominant barrier repair formulation against the topical corticosteroid 0.05% fluticasone propionate. The trial reported that eczema severity, pruritus and sleep loss improved similarly in both groups. The second study reported a significant reduction in eczema severity in the short-term with the ceramide-containing emollient compared with no emollient.

There were other topical treatments evaluated in trials including adults (10 trials), not reporting age (8 trials), or children (14 trials). See Nankervis et al. (2016) for further details.

Antimicrobials including antibiotics, antiseptics and antifungal agents

There were 16 trials on antimicrobials with 5 reporting results for children:

- A three-arm trial including children with infected eczema (aged ≥6 years, n=629) reported that a new lipid cream formulation containing fusidic acid and betamethasone 17-valerate was not inferior to a cream containing fusidic acid and betamethasone although the new lipid cream formulation was better than placebo (lipid cream alone) in the reduction of eczema severity.
- A trial including children and adults (aged 2 to 65 years, n=119) reported no difference in eczema severity between mupirocin plus hydrocortisone butyrate and hydrocortisone butyrate alone.
- A three-arm trial including infants with moderate eczema (6 months to 2 years, n=83) reported that hydrocortisone plus mupirocin was better than hydrocortisone-only or emollient-only in terms of eczema severity.
- A trial included children with moderate to severe infected eczema (aged 6 months to 17 years, n=31) reporting that eczema severity decreased more with bleach bath plus mupirocin compared to placebo.

- A within-person trial including children with severe eczema (aged 5 to 14 years, n=30) reported that there were no differences between the groups of miconazole plus 1% hydrocortisone and 1% hydrocortisone only in terms of participant reported eczema symptoms.

Antihistamines and mast cell stabilisers

Ten trials were identified, 6 of which included children. Only one study (n=114) reported greater improvement in severity of eczema with topical 4% sodium chromoglycate compared to placebo (topical lotion). In all other studies no differences between interventions and comparators were observed.

Dietary interventions

There were 42 trials, 32 of which included children or children and adults.

- Seventeen trials covered probiotics. Results were mixed with most (13 trials) reporting no significant improvement in severity of eczema and others observing significant improvement (4 trials).
- Two trials covered prebiotics with 1 reporting a significant reduction in severity of eczema in the oral kestose group compared with no treatment and another reporting no difference between groups (fructo-oligosaccharides and inulin versus placebo).
- Seven trials covered synbiotics with mixed results.
- Two trials covered essential fatty acid supplementation. One study reported that severity of eczema was significantly better with evening primrose oil compared to placebo (sunflower oil). The second trial reported no significant differences between borage oil compared to placebo on severity of eczema.
- Studies were also identified on vitamin D and E, goat's milk and hypoallergenic formula (see Nankervis et al. (2016) for further information).

Non-pharmacological interventions

There were 32 trials on non-pharmacological interventions with 25 trials including children.

- Seven trials covered specialised clothing:
  - Three studies reported some benefit of DermaSilk sleeves on severity of eczema.
  - Other materials considered to be beneficial in studies included undergarments made of anion textile (pure polyester fibres containing nanoparticles of crushed tourmaline) and silver textile with prednicarbate ointment. Other studies reported no benefits for ethylene vinyl alcohol fibre fabric or silver filaments compared to control groups.
- Six trials covered education:
  - Four trials reported that severity of eczema was significantly improved in the intervention groups (comprising an education programme in a group setting) compared to the control groups. Individual education or 2-hour training sessions were reported to be no different to controls in two studies.
- For information on the following additional interventions considered see Nankervis et al. (2016):
  - Dermatology nurse consultations
  - Support groups
  - e-health portal
  - Ion-exchange water softeners
  - House dust mite reduction
  - Living in a different climate
  - Additional visits to a doctor
  - Vaccines

Phototherapy treatment

There were 11 trials on phototherapy treatment with 3 including children.

Ultraviolet A/B treatments:

- One trial included children and adults with moderate to severe eczema (aged 8 to 45 years, n=31) reporting that severity of eczema reduced in both groups but did not report comparisons between the groups (phototherapy with UVA/UVB against phototherapy combined with topical corticosteroids).
- One trial (participants aged 5 to 17 years, n=26) reported no significant differences in severity of eczema between three groups (narrowband UVB alone, narrowband UVB in combination with 1% pimecrolimus and pimecrolimus alone).

Full-spectrum light treatments:

- This trial included children with moderate to severe eczema (n=38) and reported that severity of eczema was reduced in both groups but a between-groups comparison was not reported (full-spectrum light plus emollient against emollient alone).

Systemic immunomodulatory agents

There were 26 trials with 5 reporting results for children.

Montelukast:

- One trial (participants aged 6 to 16 years, n=15) reported that severity of eczema was decreased in both groups but there was not a comparison between the groups (montelukast against placebo).
- One trial included children and adults with atopic eczema (aged ≥6 years, n=31) reporting that severity of eczema was significantly reduced with montelukast compared with hydrocortisone and antihistamine.

Systemic immunotherapy (desensitisation):

- A trial of children and adults with eczema and sensitisation to house dust mite allergens (n=65) reported that severity of eczema improved significantly in the group receiving immunotherapy compared to standard treatment alone.

- A trial in children with chronic eczema (aged 5 to 16 years, n=56) reported that severity of eczema improved significantly in the group receiving sublingual immunotherapy using a solution containing house dust mite compared to a placebo solution but only from 9 months until trial completion at 18 months.

Intravenous immunoglobulin:

- A trial in children with moderate to severe atopic eczema (aged >2 years, n=40) reported that severity of eczema was significantly improved in the group receiving intravenous immunoglobulin compared to placebo.

Complementary therapies

In total 16 trials on complementary therapies were identified. The 5 trials including children or children and adults reported the following results:

Aromatherapy/massage:

- In children with eczema (aged 3 to 7 years, n=16), no significant differences in child's general improvement was observed between the groups (massage using essential oils in massage oil or without essential oils).

Chinese herbal medicine:

- Two trials reported no significant difference in severity of eczema among participants randomised to a five-herb concoction (moderate to severe eczema, aged 5 to 21 years, n=85) or herbal preparation of Siberian ginseng, *Achillea millefolium* and *Lamium album* (moderate eczema, aged >12 months, n=49) compared with placebo.

Other interventions:

- One trial (participants aged 2 to 17 years, n=105) compared capsules containing *P. leucotomos* extract against placebo capsules and reported that severity of eczema was not significantly different between the groups.

- A trial of balneotherapy in children with mild to moderate atopic dermatitis (aged 1 to 14 years, n=104) reported a greater reduction in severity of eczema after 2 weeks of treatment in participants in the topical corticosteroid group compared with those given balneotherapy.

Strengths and limitations

Strengths

This systematic review updates new evidence on treatments for atopic eczema included by NICE guideline CG57 and includes RCTs in children.

Limitations

It was not possible to combine data through meta-analysis. However, the lack of meta-analyses made it more difficult to draw conclusions about the different interventions for the management of atopic eczema in children.

The majority of trials did not provide sufficient information to assess the risk of bias. Some of the trials did not specify the age range when including children.

Most of the trials were small, often in less than 100 participants.

In terms of the dietary interventions section, some trials did not report a comparison between groups. These results made it difficult to draw a conclusion about dietary interventions.

For non-pharmacological interventions, systemic immunomodulatory agents and complementary therapies, many were only evaluated in single or up to 2 trials which made it difficult for the authors to draw conclusions.

The consideration of phototherapy was limited in that 2 of the trials did not provide comparisons between treatments and the other trial reported no significant differences between the comparison groups. This evidence was not enough to draw conclusions on phototherapy.

Overall impact on guideline

The authors of this systematic review noted that it was not possible to pool the data from different interventions into meta-analyses. The absence of meta-analyses made it difficult to detect a real effect or lack of effect from different interventions included in this systematic review. For most of the interventions, the included studies provided mixed results about their beneficial effect in the treatment of atopic eczema in children. The first version of this systematic review did not find evidence for all the different interventions reported in the update. In general, the available evidence was also mixed (Hoare et al. 2000). Therefore, it was considered that the update of this systematic review did not provide strong evidence to suggest a change in current recommendations of NICE guideline CG57 regarding the treatment of atopic eczema in children.

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 8 years after the publication of atopic eczema in under 12s: diagnosis and management (2007) NICE guideline CG57.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

Previous surveillance update decisions for the guideline are on our website.

New evidence

We found 24 new studies in a search for randomised controlled trials and systematic reviews published between 01 October 2013 and 17 November 2015. We also considered 27 additional studies identified by members of the Guideline Committee who originally worked on this guideline. A further study was identified through post-publication communications.

Evidence identified in previous surveillance 4 and 6 years after publication of the guideline was also considered. This included 64 studies.

From all sources, 116 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: decision matrix for summaries and references for all new evidence considered.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline and other correspondence we have received since the publication of the guideline.

Views of stakeholders

Stakeholders commented on the decision not to update the guideline and place NICE guideline CG57 on the static list. See appendix B for stakeholders' comments and our responses. Eleven stakeholders commented on this. Eight stakeholders agreed with the proposal not to update the guideline and three disagreed giving information about significant published and on-going trials. NICE guidelines make recommendations based on the best available evidence. New evidence and topic expert feedback suggested that there was new evidence related to assessment of atopic eczema severity, epidemiology, management of trigger factors, treatment, education and adherence to therapy but more work needs to be done. In the current surveillance review none of the new evidence considered was thought to have an impact on the current recommendations.

Eight stakeholders commented on the proposal to place NICE guideline CG57 on the static list. Six stakeholders agreed and two disagreed with this proposal. Given the information provided during the consultation process we decided not to place NICE guideline CG57 on the static list.

See ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual' for more details on our consultation processes.

NICE Surveillance programme project team

Sarah Willett
Associate Director

Philip Alderson
Consultant Clinical Adviser

Emma McFarlane
Technical Adviser

Yolanda Martinez
Technical Analyst

The NICE project team would like to thank the topic experts who participated in the surveillance process.