

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

Review consultation document

Review of Clinical Guideline (CG57) – Atopic eczema in children

1. Background information

Guideline issue date: 2007

4 year review: 2011

National Collaborating Centre: Women's and Children's Health

2. Consideration of the evidence

Evidence identified from initial intelligence gathering, qualitative feedback from other NICE departments, the views expressed by the Guideline Development Group, and a high-level randomised control trial (RCT) search, identified 41 studies relating to several clinical areas within the guideline scope. A large amount of the new evidence focused on treatment effectiveness of:

- Treatments for infections associated with atopic eczema
- Topical calcineurin inhibitors
- Emollients
- Phototherapy
- Probiotics (new area not included in the original guideline)

Five clinical questions relating to these areas were developed for additional focused searching. The clinical questions and the results of the focused searches are summarised in the table below. No new evidence was identified that was relevant to the research recommendations in the original guideline.

All references identified through the initial intelligence gathering, high-level RCT search and the focused searches can be viewed in [Appendix 1](#).

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Clinical area 1: Treatments for infections associated with eczema		
Clinical question	Summary of evidence	Relevance to guideline recommendations
<p>Question 1</p> <p>What is the effectiveness of antibiotics/ antimicrobials for managing and treating eczema in children?</p> <p>Relevant section of the guideline:</p> <p>7.6 Treatment for infections associated with atopic eczema</p>	<p>Through the focused search 10 studies relevant to the clinical question were identified.</p> <p><u>No beneficial effects of antimicrobials/antibiotics</u></p> <p>One meta-analysis failed to find clear evidence of benefit for antimicrobial interventions for people with atopic eczema, despite their widespread use. However the studies included in the meta-analysis were small and poorly reported. (Birnie, et al 2009).</p> <p><u>Beneficial effects of antimicrobials/antibiotics</u></p> <p>Four studies were identified:</p> <ul style="list-style-type: none"> • A meta-analysis found the effectiveness of cyclosporin is similar in adults and children, but tolerability might be better in children (Schmitt et al. 2007) 	<p>No conclusive evidence was identified that would invalidate current guideline recommendations.</p>

	<ul style="list-style-type: none"> • One study confirmed that triclosan is well tolerated and has a very low sensitizing potential even in high-risk patients affected by eczema (Schena, et al, 2008). <p><u>Silk fabrics</u></p> <p>Two studies found a beneficial effect of silk garments treated with an antibacterial agent:</p> <ul style="list-style-type: none"> • One uncontrolled study found the use of Dermasilk has a significant beneficial effect in atopic dermatitis because of the non-irritating properties of silk as well as the antibacterial capacity of AEGIS AEM 5772/5 (Koller, 2007) • One RCT study demonstrated the importance of including the AEM 5772/5 finish to the specially knitted silk for a long-term improvement of atopic eczema symptoms (Stinco 2008) <p><u>Other interventions for reducing infection</u></p> <p>One prospective, parallel, randomized study found that topical anti-inflammatory therapy alone to improve the allergic skin inflammation of AD</p>	
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	<p>can reduce <i>S aureus</i> colonization of the skin. Topical antibiotics should be reserved for short-term use in obvious secondary bacterial infection (Hung, et al. 2007)</p> <p>Overall, the identified new evidence supports current guideline recommendations that systemic antibiotics should be used to treat widespread infections and topical antibiotics should be reserved for cases of localised infection. There is still a lack of robust evidence on the effectiveness of silk fabrics treated with an antibacterial agent.</p>	
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Clinical area 2: Topical calcineurin inhibitors		
Clinical question	Summary of evidence	Relevance to guideline recommendations
<p>Question 2</p> <p>What is the effectiveness of topical calcineurin inhibitors (TCI's) for managing and treating eczema in children?</p> <p>Relevant section of the guideline:</p> <p>7.3 Topical calcineurin inhibitors</p>	<p>** Tacromilus has now been licensed for the maintenance treatment of atopic eczema to prevent flares since the guideline was published**</p> <p>Through the focused search 30 studies relevant to the clinical question were identified.</p> <p><u>Preventing flares</u></p> <p>Six studies reported Topical Calcineurin Inhibitors (TCIs) were effective at preventing flares and their use was at no additional cost for moderate eczema, and increased cost effectiveness for severe eczema (Thaci, et al. 2010; Thaci, 2008; Ruer-Mulard, 2009; Paller, 2008; Kubota, Y 2009; Healy 2011).</p> <p><u>Long term use</u></p> <p>Four studies reported that TCIs were safe and effective for long term use</p>	<p>Potential new evidence that may need to be included in the guideline.</p>

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	<p>(Zuberbier & Brautigam, 2008; Remitz, 2007; Reitamo, 2008; Langley, 2008)</p> <p><u>General safety/effectiveness</u></p> <p>10 studies found that TCI's were safe and effective, relieving itch and improving quality of life (Ring, J.,2008; Meurer, M., 2010; Kondo, Y 2009; Kirsner RS 2010; Hon 2007; Hoeger 2009; Gontijo 2008; Fowler 2007; Doss 2010; Chen 2010;).</p> <p>6 additional studies found no increase in adverse effects such as, lymphoma, systemic absorption, skin infections, and growth in children who had or were using TCIs (Yang & Curran, 2009; Reitamo, 2009; Krueger, 2007; Eitchenfield 2007; Arellano 2007; Gradman 2007)</p> <p><u>Compared to Corticosteroids</u></p> <p>One study found a TCI/FP combination regimen was equivalent to that of vehicle/FP (Spergel, 2007). One study found tacrolimus to be more effective than topical corticosteroid in 72 of the 93 children (77%) who</p>	
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	<p>completed the study (Arkwright, 2007). In patients with clinical insensitivity to CS there was a significant positive correlation between <i>S. aureus</i> and disease severity, treatment with pimecrolimus cream 1% is useful, especially in the head/neck area (Leung, 2009).</p> <p>Overall, the identified new evidence does not contradict current recommendations on the use of TCIs to treat moderate to severe atopic eczema. However, the new evidence also suggests that TCIs may be effective in preventing flares, is safe for long-term use, and more effective than corticosteroids.</p>	
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Clinical area 3: Emollients		
Clinical question	Summary of evidence	Relevance to guideline recommendations
<p>Question 3 What are the benefits and harms of using emollients for managing and treating eczema in children?</p> <p>Relevant section of the guideline: 7.1 Emollients</p>	<p>No studies were identified that specifically addressed the adverse effects of emollients for managing and treating eczema in children.</p> <p>However, the GDG provided references for a study on harms associated with aqueous creams in healthy adults (Tsang et al 2010), and an abstract on adverse reactions amongst children to aqueous creams (Cork, 2003) that was published before the cut off date for searching were identified during the initial intelligence gathering prior to conducting the focused search.</p> <p>Overall, there is still insufficient evidence to refute current recommendations on the use of emollients in children with eczema.</p>	<p>No conclusive evidence was identified that would invalidate current guideline recommendations.</p>

Clinical area 4: Phototherapy		
Clinical question	Summary of evidence	Relevance to guideline recommendations
<p>Question 4 What is the effectiveness of phototherapy for managing and treating eczema in children?</p> <p>Relevant section of the guideline: 7.8 Phototherapy and systemic treatments</p>	<p>Through the focused search one study relevant to the clinical question were identified.</p> <ul style="list-style-type: none"> • One retrospective review was identified that examined narrowband ultraviolet B (NB-UVB) phototherapy in children with atopic dermatitis (AD) who had been seen in the dermatology department between 1999 and 2005. Overall, the treatment was well tolerated and the median length of remission was 3 months (Clayton, et al 2007) <p>Overall, the new evidence identified does not contradict current recommendations on the use of phototherapy only for the treatment of severe atopic eczema in children when other management options have failed or are inappropriate.</p>	<p>No conclusive evidence was identified that would invalidate current guideline recommendations.</p>

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Clinical area 5: Probiotics		
Clinical question	Summary of evidence	Relevance to guideline recommendations
<p>Question 5</p> <p>What is the effectiveness of probiotics for managing and treating eczema in children?</p> <p>Relevant section of the guideline:</p> <p>This is a new area that is not addressed in the current guideline</p>	<p>Through the focused search 17 studies relevant to the clinical question were identified.</p> <p><u>Beneficial effect of probiotics</u></p> <p>Four studies found probiotics has a positive treatment effect:</p> <ul style="list-style-type: none"> • A meta-analysis found a modest role for probiotics in paediatric atopic dermatitis. The effect is seen in moderately severe rather than mild disease (Michail, 2008). • A systematic review found probiotics reduced the severity of AD in approximately half of the RCTs evaluated, although they were not found to change significantly most of the inflammatory markers measured in the majority of the RCTs evaluated (Betsi, et al 2008). • An RCT found that the administration of a probiotic mixture was associated with significant clinical improvement in children with AD 	<p>No conclusive evidence was identified that would enable a recommendation to be made.</p>

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	<p>(Gerasimov, 2010).</p> <ul style="list-style-type: none"> • An observational study found that an immunobiotic is safe and effective for the treatment and prevention of childhood eczema and possible other types of atopy (Hoang, 2010) <p><u>No Benefit of probiotics</u></p> <p>Six studies found that probiotics had no impact on AD, and in some cases had adverse effects:</p> <ul style="list-style-type: none"> • Two meta analyses suggested that probiotics are not an effective treatment for eczema, although one of the meta analyses noted that they may have benefit for preventing rather than treating AD, and the other meta analysis noted that probiotic treatment carries a small risk of adverse events such as bowel infections and ischaemia (Boyle et al 2008; Lee et al 2008). • A systematic review found there is not enough evidence to support the use of pro-, pre- or synbiotics for prevention or treatment of AD in children in clinical practice (van der Aa, 2010a) 	
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	<ul style="list-style-type: none">• A multi centre RCT found a symbiotic mixture does not have a beneficial effect on AD severity in infants, although it does successfully modulate their intestinal microbiota. Further randomized-controlled trials should explore a possible beneficial effect in IgE-associated AD (van der Aa, 2010b)• An RCT found that a probiotic did not improve AD significantly in children with moderate to severe disease (Brothers, 2009)• An RCT could not confirm synbiotic as an effective treatment for childhood atopic dermatitis (Shafiei, 2011) <p>Overall, there is still insufficient conclusive evidence on the effectiveness of probiotics.</p>	
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Two ongoing clinical trials (publication dates unknown) were identified. One was a Health Technology Assessment (HTA) trial focusing on antibiotics (The CREAM study), and one was a trial focusing on supporting patients and carers management of childhood eczema:

- Antibiotics: The primary aim of the HTA CREAM study is to determine whether oral or topical antibiotics, in addition to corticosteroid cream, are effective at reducing subjective eczema severity at two weeks in children with suspected infected eczema in primary care.
- Supporting the management of childhood eczema: The primary aim of this trial is to explore the concerns of parents/carers of children with eczema through qualitative interviews. A website based intervention to support self-management amongst parents/carers of children with eczema will then be developed. An RCT of the web based intervention will take place to test its effectiveness. Quality of life and progression to other atopic diseases will be measured.

Guideline Development Group and National Collaborating Centre perspective

A questionnaire was distributed to GDG members and the National Collaborating Centre to consult them on the need for an update of the guideline. Eight (47%) responses were received with respondents highlighting:

- New evidence on the potential for misuse and harms relating to aqueous creams and emollients
- A change in clinical practice now that tacrolimus has been licensed to prevent flares
- New evidence of the benefits and harms of antimicrobial/antibiotic products

These three areas were worked up into focused questions in order to further explore these issues. In addition the GDG also mentioned:

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- Variation in access to allergy services, how eczema treatments are combined, and how treatments are stepped up or down
- Safety issues were raised in regard to natural topical products that are available over the internet

Two respondents stated that the guideline should be updated in order to reduce variation in current practice, and two considered that the guideline did not warrant an update at this time suggesting waiting for further evidence regarding the role of weaning diets, food allergy, and the role of fillagrin in the development of eczema.

Implementation and post publication feedback

In total 25 enquiries were received from post-publication feedback, most of which were routine. Key themes emerging from post-publication feedback included:

- lack of guidance around the ineffectiveness of emollients
- lack of clarity around who can treat or prescribe
- lack of consideration for phototherapy.

This feedback contributed towards the development of the clinical questions as described above.

No specific feedback from the implementation team was provided, other than an audit of uptake of the guidance was published in the BMJ, showing that the information given to patients was highly variable.

Relationship to other NICE guidance

The following NICE guidance is related to CG57:

Guidance	Review date
TA81: <i>Frequency of application of topical corticosteroids for eczema</i>	Publication date: August 2004 To be reviewed: TBC

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TA82: <i>Pimecrolimus and tacrolimus for atopic dermatitis (eczema)</i>	Publication date: August 2004 To be reviewed: January 2009
Related NICE guidance not included in CG57	
CG116: Food allergy in children and young people	Publication date: February 2011 To be reviewed 2014.
IPG236: <i>Grenz rays therapy for inflammatory skin conditions</i>	Publication date: November 2007 To be reviewed: TBC
TA177: <i>Alitretinoin for the treatment of severe chronic hand eczema</i>	Publication date: August 2009 To be reviewed: August 2012
Related NICE guidance in progress	
Psoriasis	Currently in development: Wave 23 Publication date: TBC.

Anti-discrimination and equalities considerations

No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope is inclusive of children from birth up to the age of 12 years with atopic eczema.

Conclusion

From the evidence and intelligence identified through the process, it suggests that there are developments in some areas of the guideline, particularly in relation to:

- Treatment of atopic eczema with Topical Calcineurin Inhibitors (TCIs). The licensing of this intervention has changed since the current guideline was published, and studies identified in the focused search have provided evidence for its safety and efficacy for preventing flares and its long term use, which is not covered in the current guideline.

This is a small area of the guideline, and may not be significant enough to warrant updating the guideline at this point. It also may be pertinent to await further evidence, particularly on the harms associated with emollients, before an update is commissioned. These areas will be factored into the future reviews.

3. Review recommendation

The guideline should not be updated at this time.

The guideline will be reviewed again according to current processes.

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May 2011

Appendix I: Focused search references

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