NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

Review of Clinical Guideline (CG57) – Management of 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. Review recommendation

- The guideline should not be updated at this time.

3. Factors influencing the decision

Literature search

1. 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 related to the following clinical areas within the guideline:
    - Treatment for infections associated with atopic eczema
    - Topical Calcineurin Inhibitors
    - Emollients
    - Phototherapy
    - Probiotics (new area not included in the original guideline)

2. Five clinical questions were developed based on the clinical areas above, qualitative feedback from other NICE departments and the views expressed by the Guideline Development Group, for more focused literature searches. In total, 47 studies were identified through the focused searches.

3. Currently the guideline incorporates recommendations from TA82 Pimecrolimus and tacrolimus for atopic dermatitis (eczema). A licence change and new evidence was found in relation to this TA:
    - The licensing for tacrolimus changed in 2009 enabling it to be used for the maintenance treatment of moderate to severe atopic dermatitis for the prevention of flares and prolongation of flare free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times a year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared or mildly affected). This indication is additional to that already obtained and appraised in TA82 for the treatment of moderate to severe atopic dermatitis in adults and children 2 years of age and above who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids.
    - The Centre for Health Technology Evaluation considered this licence extension and concluded this would not necessitate a review of TA82 since the population reflected in the licence extension will already have this topical cream to treat their condition on an intermittent basis.

4. No evidence was identified which directly answered the research recommendations presented in the original guideline.

5. An ongoing clinical trial was identified:
    - Health Technology Assessment trial of antibiotics (The CREAM study). This 3 year trial aims to determine whether oral or topical

antibiotics, in addition to corticosteroid cream, are effective at reducing eczema severity in children with suspected infected eczema. The trial will begin in January 2012

Guideline Development Group and National Collaborating Centre perspective

6. 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 responses were received with respondents highlighting that since publication of the guideline more literature has become available on:
    - The potential for harms relating to aqueous creams
    - A change in clinical practice now that tacrolimus has been licensed as a second line treatment to prevent flares in moderate to severe cases of atopic eczema
    - New evidence of the benefits and harms of antimicrobial/antibiotic products

    This feedback contributed towards the development of the clinical questions for the focused searches.

7. Newly published and ongoing research was cited by GDG members including:
    - One very small study relating to the adverse effects of aqueous creams in adults.
    - An ongoing trial evaluating whether emollient application from birth can prevent the development of eczema, with an arm that is also investigating the potential harmful effect of emollients on the skin barrier- The BEEP study (Feasibility Study of Barrier Enhancement for Eczema Prevention).
    - An ongoing trial exploring the concerns of parents/carers of children with eczema, and the effectiveness of a website based intervention to support self-management.

8. Two respondents stated that the guideline should be updated in order to reduce variation in current practice, and two stated 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

9. Key themes emerging from post-publication feedback were:
    - General enquiries about the guideline
    - Lack of guidance regarding the harms of aqueous creams
    - Lack of clarity around who should treat/prescribe

10. An analysis by the NICE implementation team indicated the standard of information provision to patients and parents was variable.

    This feedback contributed towards the development of the clinical questions for the focused searches.

Relationship to other NICE guidance

11. NICE guidance related to CG57 can be viewed in Appendix 1.

Summary of Stakeholder Feedback

Review proposal put to consultees:
The guideline should not be updated at this time.
The guideline will be reviewed again according to current processes.

12. In total 13 stakeholders commented on the review proposal recommendation during the 2 week consultation period. Comments can be viewed in Appendix 2.

13. Three stakeholders agreed with the decision not to update, 4 disagreed with the decision, and the 6 remaining stakeholders did not state a definitive decision.

14. Stakeholders who disagreed felt that the following areas should be considered for update:
    - Topical Calcineurin Inhibitors for maintenance and prevention of flares: some stakeholders felt there was enough evidence regarding the license change for tacrolimus to warrant an update of the guideline at this time, and that this would be of benefit to GPs. Currently, the guideline incorporates the recommendations from TA82 that pimecrolimus and tacrolimus should be used within their licensed indications as second line treatments when conventional therapies have failed. Long term safety data is still lacking and there are ongoing trials that aim to address this. Therefore the existing guideline recommendations still stand.
    - Emollients: stakeholders felt that the evidence regarding the potential harms of aqueous creams (one type of emollient) requires an update of the guideline. However the evidence came from 3 very small studies that were all conducted on adults, and on anecdotal evidence provided by GDG members and post publication feedback. A large ongoing study that is recruiting from the BEEP trial is investigating the effects of emollients on the skin barrier. The estimated completion date for this study is January 2012.

15. Literature was submitted through stakeholder consultation relating to:
    - The harmful effects of aqueous creams, published in June 2011
    - The role of allergy in eczema (these studies were considered outside the scope of the current guideline).
    - An ongoing evaluation of the long term safety of tacrolimus ointment in children (10 year follow up study)- The APPLES trial
    - An ongoing 10 year registry evaluation of the safety of pimecrolimus 1% in children- The PEER trial

16. During consultation, stakeholders suggested new areas to consider in an update of the guideline including:

- The role of fillagrin in eczema
- The links between food allergy and eczema
- Widening the scope to include preventing eczema in infants. However this is outside of the remit of the guideline
- Widening the scope to include allergic contact dermatitis. However this is outside of the remit of the guideline

Anti-discrimination and equalities considerations

17. No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope includes the management of children from birth up to the age of 12 years presenting with atopic eczema, in primary secondary or community care.

Conclusion

18. From the evidence and intelligence identified through the process, it suggests that one area of the guideline- the use of aqueous creams as emollients- may need updating in due course if more substantial evidence becomes available.

19. The guideline should not be considered for an update at this time.

Relationship to quality standards

20. This topic is not currently being considered for a quality standard.

Fergus Macbeth – Centre Director
Sarah Willett – Associate Director
Sheryl Warttig – Technical Analyst
Centre for Clinical Practice

19 July 2011

APPENDIX 1

The following NICE guidance is related to CG57:

Guidance	**Review date**
TA81: Frequency of application of topical corticosteriods for eczema	Publication date: August 2004 To be reviewed: TBC
TA82: Pimecrolimus and tacrolimus for atopic dermatitis (eczema)	Publication date: August 2004 Reviewed: June 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: Grenz rays therapy for inflammatory skin conditions	Publication date: November 2007 To be reviewed: TBC
TA177: Alitretinoin for the treatment of severe chronic hand eczema	Publication date: August 2009 To be reviewed: August 2012
Related NICE guidance in progress	
Psoriasis	Currently in development: Wave 23 Publication date: TBC.

APPENDIX 2

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

CG57 Atopic eczema in children

Guideline Review Consultation Comments Table

23 May – 3 June 2011

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
Astellas Pharma Ltd	Disagree	With reference to clinical area 2: Topical Calcineurin Inhibitors. Astellas consider that the extension of the license of topical calcineurin inhibitors to include maintenance treatment warrants an update to the guideline. There is evidence that the preventative use of tacrolimus ointment (Protopic) reduces the number of flares and prolongs the time spent free from flares in children, at no additional cost in patients with moderate eczema, and may be cost saving in those with severe eczema. (Thaci 2008, Thaci 2010).			Thank you. The studies that you have mentioned were included in the review. Although there is some new evidence to support the license extension of Tacrolimus, this does not contradict the existing guideline recommendations.
The British Dietetic		We do not have any comments at this stage. We would however, be			Thank you.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
Association (BDA)		grateful if you could inform us of the outcome of the consultation and of any further consultations.			
British Association of Dermatologists	Agree	In due course, the role of topical tacrolimus as a maintenance therapy should be included.		None	Thank you. The role of calcineurin inhibitors will be monitored.
British Association of Dermatologists	Agree		The value of probiotics has not been established. Mention of this is made in the SIGN guideline on atopic eczema.		Currently the evidence base for probiotics is too heterogeneous to enable any recommendations about the value of probiotics to be made.
British Society for Cutaneous Allergy			Section 6.2. Why was diagnosis of allergic contact dermatitis excluded from the original scope? Particularly in the older child indications for patch testing in this patient group may be helpful to identify relevant triggers and improve patient		The remit of the guideline which was provided by the Department of Health was to specifically focus on atopic eczema in children, and to exclude other types of dermatitis. If the contact dermatitis were to be considered by NICE, it would be in a separate guideline, not in a review of CG75 Atopic eczema in children.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
			care. Could this be considered an area for future review?		
British Society for Allergy and Clinical Immunology (BSACI)	Need to reference as strengthens existing proposal	Hill DJ, Hosking C, de Benedictis FM, Oranje AP, Diepgen TL, Bauchau V. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. Clin Exp Allergy 2008;38(1):161–8.	Adds further weight to statements regarding the suspicion of co-existing food allergy in infants with moderate to severe eczema. It expands on this adding the concept of age of eczema onset being an important factor in teasing out whether food allergy may be important with those with eczema onset < 3 months being at greatest risk and		Thank you. Recommendations already exist in relation to the co-existence of food allergy in children with eczema in the current guideline. The NICE Food Allergy guideline (CG116) also specifically provides recommendations on diagnosing food allergy in a primary care setting.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
			those with eczema onset > 12 months being at least risk.		
British Society for Allergy and Clinical Immunology (BSACI)	Need to reference	NICE guideline in food allergy Feb 2011	Underscores that eczema is a risk factor for food allergy		Thank you. The NICE Food Allergy guideline (CG116) is linked to the eczema guideline on the NICE website and will be cross referred.
British Society for Allergy and Clinical Immunology (BSACI)	Need to reference	RCPCH care pathways for eczema	Highlights the importance of diagnosing food and inhalant allergy especially in infants and children with moderate to severe eczema. Emphasises that severe eczema is a multisystem disease.		Thank you.
British Society for Allergy and Clinical Immunology (BSACI)	Need to reference	Wahn U, Warner J, Simons FE et al. IgE antibody responses in young children with atopic dermatitis. Pediatr Allergy Immunol 2008;19(4):332–6.	Emphasises that the risk of food allergy to eczema of all severity is much lower than		Thank you. Recommendations already exist in relation to the co-existence of food allergy in children with eczema in the current guideline. The NICE Food Allergy

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
			in children with eczema selected on the basis of severity.		guideline (CG116) also specifically provides recommendations on diagnosing food allergy in a primary care setting.
British Society for Allergy and Clinical Immunology (BSACI)	Need to reference but does not change recommendation	Vandenplas Y, Brueton M, Dupont C et al. (2007) Guidelines for the diagnosis and management of cow's milk protein allergy in infants. Archives of Disease in Childhood 92: 902-8.	Adds support to statements in original guideline regarding choice of formula and advice re maternal exclusion diets in breast feeding mothers. This statement was not included in SIGN and is such an important one to emphasise.		Thank you.
British Society for Allergy and Clinical Immunology (BSACI)	The section on epidemiology could be strengthened	Lowe A, Hosking C, Bennett CM et al. Skin prick test can identify eczematous infants at risk of asthma and allergic rhinitis. Clin Exp Allergy 2007;37(11):1624–31.	Highlights the risk factors of infants with eczema developing asthma and allergic rhinitis. Emphasises the value of skin prick		Thank you.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
			testing in identifying high risk infants.		
British Society for Allergy and Clinical Immunology (BSACI)		Jensen C (20090: The association between early sensitization patterns and subsequent allergic disease. The DARC birth cohort study. Paediatric Allergy and Immunology 20, 726-734	The section on epidemiology could be strengthened		Thank you.
British Society for Allergy and Clinical Immunology (BSACI)		Schroeder A et al (2009): Food allergy is associated with an increased risk of asthma. Clin and Experimental Allergy 261-270	The section on epidemiology could be strengthened		Thank you.
British Society for Allergy and Clinical Immunology (BSACI)	Needs updating or reference to NICE food allergy and RCPCH care pathways	Referral for specialist care – see NICE food allergy consider referral to secondary or specialist care in any of the following circumstances. significant atopic eczema where multiple or cross-reactive food allergies are suspected by the parent or carer. • There is: − persisting parental suspicion of	The current guideline makes no recommendations about referral for allergy evaluation or allergy testing. The guideline considers food allergy but gives no guidance on what to do once food allergy is considered. This		Thank you. Referral for allergy testing is covered by the NICE food allergy guideline (CG116). This will be linked to the eczema guideline on the NICE website and will be cross referred. NICE does not recommend other organisations pathways or guidelines such as those from RCPCH.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
		food allergy (especially in children or young people with difficult or perplexing symptoms) despite a lack of supporting history − strong clinical suspicion of IgE-mediated food allergy but allergy test results are negative − clinical suspicion of multiple food allergies.	is now covered in NICE food allergy and RCPCH care pathways		
British Society for Allergy and Clinical Immunology (BSACI)		Marenholz I, Kerscher T, Bauerfeind A et al (2009). An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. J Allergy Clin Immunol; 123; 911-6	Will the section on fillagrin be covered? It does provide a compelling link between barrier disruption, allergic sensitiation and certain phenotypes of asthma.		Thank you. Currently there is limited evidence on the role of fillagrin in eczema. This will be assessed again at the next review
Department of Health		I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation.			Thank you
LEO Pharma	Agree	Thank you for the opportunity to comment on this proposal. We			Thank you.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
		agree that developments in this clinical area have not been sufficient enough to warrant updating the guideline.			
Nottingham Support Group for Carers of Children with Eczema (NSGCCE)	No	Question 3 What are the benefits and harms of using emollients for managing and treating eczema in children? We are surprised that in a guideline which places emollients firmly as the universal treatment upon which other treatments may or may not build, that such a potentially significant finding as the potential adverse effects of aqueous cream (which is the emollient of default for many primary care practitioners) are not thought significant enough to issue a revision or an appendix to the current guidelines. The majority of children with eczema are treated in primary care. That the studies do not specifically mention children should not undervalue their significance. To ignore this may be condemning many children to worse eczema			Thank you. We did not find any studies relating to the harmful effects of aqueous creams in our searching. We were aware of one small study in adults, and have since been made aware of more recent research in adults, also from very small studies. Since the evidence base is so small we feel it would be pertinent to wait for further research from larger studies before considering changing recommendations.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
		and atopic march.			
Primary Care Dermatology Society (PCDS)	Disagree	We are disappointed that the role of topical immunomodulators will not be re-asessed in the light of the safety and prevention of flare studies. The existing guidance is restrictive especially for GP prescribing especially in the light of longer term use.			Thank you. Although there is some new evidence to support the license extension of Tacrolimus, this does not contradict the existing guideline recommendations.
Primary Care Dermatology Society (PCDS)	Disagree	The evidence regarding Aqueous cream and its problems is urgently needing review at a time when the pressure on costs is restricting choice of emollient to the detriment of patient care.		Variation in different PCT areas restrict emollient prescribing, penalising some areas and not others.	Thank you. The evidence base for the harmful effects of aqueous creams was very small, and we feel that an update at this time would be premature.
Royal College of Paediatric and Child Health (RCPCH)	There was a difference of opinion among commentators as to whether the guideline update can be deferred,				Thank you for your response

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
	and if so if should be within two years.				
Royal College of Paediatric and Child Health (RCPCH)		The main issue that should be addressed is the use of topical calcineurin inhibitors (TCIs) versus topical corticosteroids. As evidence increases on safety and efficacy of TCIs there is a need for more guidance as to which should be used in mild to moderate disease. There is currently considerable diversity of practice which must be addressed.			Thank you. TCIs are still recommended as a second line treatment to be used when conventional therapies such as corticosteroids have failed. TA82 recommends Tacrolimus for moderate to severe disease and Pimecrolimus for mild to moderate disease. Although a large amount of evidence was found during searching, the majority of it provided support for existing recommendations. There is insufficient evidence at present to address TCIs as first line treatments, or to make more prescriptive recommendations at this time.
Royal College of Paediatric and Child Health (RCPCH)		We think that an update would be useful regarding the approval of topical calcineurin inhibitors (TCIs) for preventative use, and on the irritant effect of aqueous cream (which is not normally			Thank you. TCIs are licensed for the prevention of flares in children with uncontrolled eczema, and the current guideline recommends that TCIs should be used within their licensed indications. Insufficient

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
		recommended by dermatologists as an emollient but as a soap substitute).			evidence was found on the irritant effects of aqueous cream, although this will be monitored as new evidence becomes available, particularly from the BEEP trial.
Royal College of Paediatric and Child Health (RCPCH)		We agree that there is a need for further evidence on the role of fillagrin, weaning diet, and particularly the role of food allergy where there is variation in practice across the UK.			Thank you. The evidence base relating to these areas is small at present. The guideline will be considered for update in due course as more evidence emerges.
Royal College of Paediatric and Child Health (RCPCH)		The comments regarding the Dermasilk garments are conflicting. The papers reviewed support these garments but the conclusion does not.			Thank you. Only two papers considered dermasilk. Although both found a beneficial effect the limited evidence meant that no conclusions could be drawn.
Royal College of Paediatric and Child Health (RCPCH)		The conclusions on use for flares and long term use of cyclosporin are useful additions.			Thank you.
Royal College of Paediatric and Child Health (RCPCH)		A prospective study on the clinical impact of phototherapy would be helpful.			Thank you.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
Royal College of Paediatric and Child Health (RCPCH)		An area for study is the use of topical steroids on two consecutive days to prevent flares.			Thank you.
Royal College of Paediatric and Child Health (RCPCH)			More recent publications on the importance of allergy to the disease process, particularly in infants.		
Royal College of General Practitioners (RCGP)		I think GP's would value advise on maintainance of AE with TCI's with reassurance of safety for long term use as they are not currently widely used in Primary Care probably because of concerns about safety.			Thank you. Although there is new evidence that supports the license extension of Tacrolimus, this does not contradict the existing guideline recommendations.
Royal College of Nursing	No objections to the proposal	The previous systematic review of clinical trials (Hoare et al 2000) which covers all treatments for atopic eczema has been updated. 'The Global Resource of Eczema Trials (GREAT) database holds records, including the full citation, for all randomised controlled trials on eczema treatment from the year 2000 and will be regularly updated.			Thank you. The GREAT database was reviewed for studies that were relevant for this review and were included as appropriate.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
		The database can be accessed free of charge at http://www.greatdatabase.org.uk			
Previous GDG member		The previous systematic review of clinical trials (Hoare et al 2000) which covers all treatments for atopic eczema has been updated. 'The Global Resource of Eczema Trials (GREAT) database holds records, including the full citation, for all randomised controlled trials on eczema treatment from the year 2000 and will be regularly updated. The database can be accessed free of charge at http://www.greatdatabase.org.uk			Thank you. The GREAT database was reviewed for studies that were relevant for this review and were included as appropriate.
TIPS Ltd	Disagree	There is a distinct lack of information regarding the involvement of health professionals, especially midwives, in the promotion of safe skincare guidelines in the neonatal period. Conversely there is a heavy emphasis on the promotion of pharmaceutical preparations which, in my experience, can exacerbate skin conditions.			Thank you. Preventing the development of eczema is outside of the remit of this guideline which was provided by the Department of Health to specifically focus on the management of atopic eczema. Prevention is only addressed in the context of preventing flares and advancement of the established disease.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
		An important step in the avoidance of atopic eczema is for parents to follow simple guidelines from birth which have the ability to greatly reduce the incidence and development of neonatal skin conditions of which atopic eczema is one example. The avoidance of baby skincare products in the neonatal period should be advocated in the Atopic eczema guidelines so as to be consistent with the advice given in the Postnatal Care guidelines (NICE 2006) and online at NHS Choices. Baby skincare products should be mentioned specifically alongside soaps and detergents within 'potential trigger factors'.			
TIPS Ltd	Disagree	Vernix Caseosa (VC) is a highly sophisticated bio-film consisting of antimicrobial peptides/proteins and fatty acids present at birth. These combine to form a protective barrier that is not only antibacterial but also antifungal. A study by Tollin et al (2005) goes further by stating that; " *studies confirm that*			Thank you. Whilst this is important, it relates to the area of prevention and is therefore outside the guideline.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Response
		maintaining an intact epidermal barrier by minimizing exposure to soap and by not removing VC are simple measures to improve skin barrier function". I feel it is important to highlight the importance of this remarkable substance and its relevance to neonatal skincare along with its potential to reduce the incidence of future cases of Atopic eczema in infants and young children.			