

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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23rd May – 3rd June

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| Clinical area 1: Treatments for infections associated with eczema | | |
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| 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> |

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| | <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 | | |
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| 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 | | |
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| 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 | | |
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| 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 | | |
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| 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 |
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| 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

Arellano, F.M., Wentworth, C.E., Arana, A., Fernandez, C., & Paul, C.F. 2007. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *Journal of Investigative Dermatology*, 127, (4) 808-816

Arkwright PD, G.M.E.C.D.T. 2007. Blinded side-to-side comparison of topical corticosteroid and tacrolimus ointment in children with moderate to severe atopic dermatitis. *Clinical and Experimental Dermatology* , 32, (2) 145-7TN

Betsi, G.I., Papadavid, E., & Falagas, M.E. 2008. Probiotics for the treatment or prevention of atopic dermatitis: a review of the evidence from randomized controlled trials. [Review] [63 refs]. *American Journal of Clinical Dermatology*, 9, (2) 93-103

Birnie, A.J., Bath-Hextall, F.J., Ravenscroft, J.C., & Williams, H.C. 2009. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema [Systematic Review]. *Cochrane Database of Systematic Reviews* (1)

Boyle, R.J., Bath-Hextall, F.J., Leonardi-Bee, J., Murrell, D.F., & Tang, M.L. 2009. Probiotics for treating eczema [Systematic Review]. *Cochrane Database of Systematic Reviews* (1)

Brothers S, A.M.J. 2009. Effect of a *Mycobacterium vaccae* derivative on paediatric atopic dermatitis: a randomized, controlled trial. *Clinical and experimental dermatology*. (7)

Chen, S.-L., Yan, J., & Wang, F.-S. 2010. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: A meta-analysis of randomized clinical trials. *Journal of Dermatological Treatment*, 21, (3) 144-156

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Clayton, T.H., Clark, S.M., Turner, D., & Goulden, V. 2007. The treatment of severe atopic dermatitis in childhood with narrowband ultraviolet B phototherapy. *Clinical and Experimental Dermatology*, 32, (1) 28-33

Doss, N. 2010. Efficacy of tacrolimus 0.03% ointment as second-line treatment for children with moderate-to-severe atopic dermatitis: evidence from a randomized, double-blind non-inferiority trial vs. fluticasone 0.005% ointment. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. (2 Pt 1)

Eichenfield, L.F., Ho, V., Matsunaga, J., Leclerc, P., Paul, C., & Hanifin, J.M. 2007. Blood concentrations, tolerability and efficacy of pimecrolimus cream 1% in Japanese infants and children with atopic dermatitis. *Journal of Dermatology*, 34, (4) 231-236

Fowler, J. 2007. Improvement in pruritus in children with atopic dermatitis using pimecrolimus cream 1%. *Cutis; cutaneous medicine for the practitioner*, 79, (1) 65-72

Gerasimov, S.V., Vasjuta, V.V., Myhovych, O.O., & Bondarchuk, L.I. 2010. Probiotic supplement reduces atopic dermatitis in preschool children: a randomized, double-blind, placebo-controlled, clinical trial. *American Journal of Clinical Dermatology*, 11, (5) 351-361

Gontijo, B., Pires, M.C., Cestari, T.F., La Scala, C.S.K., Duarte, I.A.G., Takaoka, R., Aun, W.T., De Souza, J.A., Cestari, S.S.D.C., & De Oliveira, Z.N.P. 2008. Evaluate of the efficacy and safety of tacrolimus ointment 0, 03% to treat atopic dermatitis in pediatric patients. [Portuguese] *Anais Brasileiros de Dermatologia*, 83, (6) 511-

Gradman, J. 2007. Short-term growth in children with eczema during treatment with topical mometasone furoate and tacrolimus. *Acta paediatrica (Oslo, Norway : 2007)* 96, (8) 1233-1237

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Healy, E., Bentley, A., Fidler, C., & Chambers, C. 2011. Cost-effectiveness of tacrolimus ointment in adults and children with moderate and severe atopic dermatitis: Twice-weekly maintenance treatment vs. standard twice-daily reactive treatment of exacerbations from a third party payer (U.K. National Health Service) perspective. *British Journal of Dermatology*, 164, (2) 387-395

Hoang, B.X., Shaw, G., Pham, P., & Levine, S.A. 2010. Lactobacillus rhamnosus cell lysate in the management of resistant childhood atopic Eczema. *Inflammation and Allergy - Drug Targets*, 9, (3) 192-196

Hoeger PH, L.K.J. 160. The treatment of facial atopic dermatitis in children who are intolerant of, or dependent on, topical corticosteroids: a randomized, controlled clinical trial. *The British journal of dermatology*. (2)

Hon KL, 2007. Efficacy and tolerability of a Chinese herbal medicine concoction for treatment of atopic dermatitis: a randomized, double-blind, placebo-controlled study. *The British journal of dermatology*. (2)

Hung S-H, Lin Y-T, Chu C-Y et al. (2007) Staphylococcus colonization in atopic dermatitis treated with fluticasone or tacrolimus with or without antibiotics. *Annals of Allergy, Asthma and Immunology* 98: 51-6.

Kirsner RS, H.M.A. 2010. Safety and efficacy of tacrolimus ointment versus pimecrolimus cream in the treatment of patients with atopic dermatitis previously treated with corticosteroids. *Acta dermato-venereologica*, 90, (1) 58-64

Koller DY, H.G. 2007. Action of a silk fabric treated with AEGIS in children with atopic dermatitis: a 3-month trial. *Pediatric allergy and immunology* : official publication of the European Society of Pediatric Allergy and Immunology, 18, (4) 335-338

Kondo, Y., Nakajima, Y., Komatsubara, R., Kato, M., Hirata, N., Matuyama, H., Kakami, M., Tsuge, I., Ohya, Y., & Urisu, A. 2009. Short-term efficacy of CG57: Eczema, review proposal consultation document

tacrolimus ointment and impact on quality of life. *Pediatrics International*, 51, (3) 385-389

Krueger, G.G., Eichenfield, L., Goodman, J.J., Krafchik, B.R., Carlin, C.S., Pang, M.L., Croy, R., Holum, M.E., Jaracz, E., Sawamoto, T., & Keirns, J. 2007. Pharmacokinetics of tacrolimus following topical application of tacrolimus ointment in adult and pediatric patients with moderate to severe atopic dermatitis. *Journal of drugs in dermatology : JDD*, 6, (2) 185-193

Kubota, Y., Yoneda, K., Nakai, K., Katsuura, J., Moriue, T., Matsuoka, Y., Miyamoto, I., & Ohya, Y. 2009. Effect of sequential applications of topical tacrolimus and topical corticosteroids in the treatment of pediatric atopic dermatitis: An open-label pilot study. *Journal of the American Academy of Dermatology*, 60, (2) 212-217 (Staab et al. 2006)

Langley RG, Eichenfield LF, Lucky AW et al. (2008) Sustained efficacy and safety of pimecrolimus cream 1% when used long-term (up to 26 weeks) to treat children with atopic dermatitis. *Pediatric Dermatology* 25: 301-7.

Larsen FS, Simonsen L, Melgaard A, Wendicke K, Henriksen AS. 2007 An efficient new formulation of fusidic acid and betamethasone 17-valerate (fucicort lipid cream) for treatment of clinically infected atopic dermatitis *Acta Derm Venereol* ;87(1):62-8.

Lee, J., Seto, D., & Bielory, L. 2008. Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. *Journal of Allergy & Clinical Immunology*, 121, (1) 116-121

Leung DY, 2009. Effects of pimecrolimus cream 1% in the treatment of patients with atopic dermatitis who demonstrate a clinical insensitivity to topical corticosteroids: a randomized, multicentre vehicle-controlled trial. *The British journal of dermatology*, 161, (2) 435-443

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Meurer, M., Lubbe, J., Kapp, A., & Schneider, D. 2007. The role of pimecrolimus cream 1% (Elidel) in managing adult atopic eczema. *Dermatology*, 215, (SUPPL. 1) 18-26

Michail, S.K., Stolfi, A., Johnson, T., & Onady, G.M. 2008. Efficacy of probiotics in the treatment of pediatric atopic dermatitis: a meta-analysis of randomized controlled trials. *Annals of Allergy, Asthma, & Immunology*, 101, (5) 508-516

Paller AS, 2008. Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. *Pediatrics*. (6)

Reitamo, S., Rustin, M., Harper, J., Kalimo, K., Rubins, A., Cambazard, F., Brenninkmeijer, E.E.A., Smith, C., Berth-Jones, J., Ruzicka, T., Sharpe, G., Taieb, A., De, R.L., Groonhooj-Larsen, C., Remitz, A., Turjanmaa, K., Perrot, J.L., Boralevi, F., Dubertret, L., Lahfa, M., Misery, L., De, P.Y., Bodemer, C., Stadler, J.F., Barbarot, S., Plantin, P., Schoenlaub, P., Lorette, G., Khallouf, R., Beylot, C., Bruckner-Tuderman, L., Wollenberg, A., Kamann, S., Kapp, A., Fartasch, M., Folster-Holst, R., Bieber, T., Ring, J., Dobozy, A., Kemeny, L., Murphy, G., Barry, J., Bourke, J., Valdmane, N., Blaszczyk, M., Wolska, H., Bos, J., Carralero, L., Carrera, C., Martinez, C., Pichardo, A.R., De, F.O., Uceda, E.S.L., Waite, A., Green, A., Friedmann, P., Finlay, A., & Griffiths, C. 2008. A 4-year follow-up study of atopic dermatitis therapy with 0.1% tacrolimus ointment in children and adult patients. *British Journal of Dermatology*, 159, (4) 942-951

Reitamo S, Mandelin J, Rubins A et al. (2009) The pharmacokinetics of tacrolimus after first and repeated dosing with 0.03% ointment in infants with atopic dermatitis. *International journal of dermatology* 48: 348-55

Remitz, A., Harper, J., Rustin, M., Goldschmidt, W.F.M., Palatsi, R., Van Der Valk, P.G.M., Sharpe, G., Smith, C.H., Dobozy, A., & Turjanmaa, K. 2007.

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Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. *Acta dermato-venereologica*, 87, (1) 54-61

Ring, J., Abraham, A., De, C.C., Kim, K., Langeland, T., Parra, V., Pigatto, P., Reunala, T., Szczepanski, R., Mohrenschlager, M., Brautigam, M., Rossi, A.B., Meents-kopecky, E., & Schneider, D. 2008. Control of atopic eczema with pimecrolimus cream 1% under daily practice conditions: Results of a > 2000 patient study. *Journal of the European Academy of Dermatology and Venereology*, 22, (2) 195-203

Ruer-Mulard, M. 2009. Twice-daily versus once-daily applications of pimecrolimus cream 1% for the prevention of disease relapse in pediatric patients with atopic dermatitis. *Pediatric dermatology*, 26, (5) 551-558

Schena, D., Papagrigoraki, A., & Girolomoni, G. 2008. Sensitizing potential of triclosan and triclosan-based skin care products in patients with chronic eczema. *Dermatologic Therapy*, 21, Suppl-8

Schmitt, J., Schmitt, N., & Meurer, M. 2007. Cyclosporin in the treatment of patients with atopic eczema - a systematic review and meta-analysis. [Review] [56 refs]. *Journal of the European Academy of Dermatology & Venereology*, 21, (5) 606-619

Shafiei, A., Moin, M., Pourpak, Z., Gharagozlou, M., Aghamohamadi, A., Sajedi, V., Soheili, H., Sotoodeh, S., & Movahedi, M. 2011. Synbiotics could not Reduce the Scoring of Childhood Atopic Dermatitis (SCORAD): A Randomized Double Blind Placebo-Controlled Trial. *Iranian Journal of Allergy Asthma & Immunology*, 10, (1) 21-28

Spergel, J.M. 2008. Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: A randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle. *Pediatrics*, 122, (SUPPL. 4) S199

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Stinco, G. 2008. A randomized double-blind study to investigate the clinical efficacy of adding a non-migrating antimicrobial to a special silk fabric in the treatment of atopic dermatitis. *Dermatology (Basel, Switzerland)*, 217, (3) 191-195

Thaci, D. 2008. Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. *The British journal of dermatology*, 159, (6) 1348-1356

Thaci, D., Chambers, C., Sidhu, M., Dorsch, B., Ehlken, B., & Fuchs, S. 2010. Twice-weekly treatment with tacrolimus 0.03% ointment in children with atopic dermatitis: Clinical efficacy and economic impact over 12 months. *Journal of the European Academy of Dermatology and Venereology* , 24, (9) 1040-1046

van der Aa, L.B., Heymans, H.S., van Aalderen, W.M., Sillevius Smitt, J.H., Knol, J., Ben, A.K., Goossens, D.A., Sprikkelman, A.B., & Synbad Study Group 2010. Effect of a new synbiotic mixture on atopic dermatitis in infants: a randomized-controlled trial. *Clinical & Experimental Allergy* , 40, (5) 795-804

van der Aa, L.B., Heymans, H.S.A., Van Aalderen, W.M.C., & Sprikkelman, A.B. 2010. Probiotics and prebiotics in atopic dermatitis: Review of the theoretical background and clinical evidence: Review Article. *Pediatric Allergy and Immunology*, 21, (2 PART 2) e355-e367

Yang, L.P.H. & Curran, M.P. 2009. Topical pimecrolimus: A review of its use in the management of pediatric atopic dermatitis. *Pediatric Drugs*, 11, (6) 407-426

Zuberbier, T. & Brautigam, M. 2008. Long-term management of facial atopic eczema with pimecrolimus cream 1% in paediatric patients with mild to moderate disease. *Journal of the European Academy of Dermatology and Venereology*, 22, (6) 718-721

CG57: Eczema, review proposal consultation document

High level search references

Abramovits, W. 2008. Hydrocortisone butyrate 0.1% lipocream in pediatric patients with atopic dermatitis. *Skinmed.* (2)

Baranzoni, N., Scalone, L., Mantovani, L.G., De, P.S., Monzini, M.S., & Giannetti, A. 2007. Validation of the Italian version of the Infants' Dermatitis Quality of Life and Family Dermatitis Indexes. *Giornale Italiano di Dermatologia e Venereologia*, 142, (5) 423-432

Bath-Hextall, F., Delamere, F.M., & Williams, H.C. 2008. Dietary exclusions for established atopic eczema. [Review] [67 refs]. *Cochrane Database of Systematic Reviews* (1) CD005203

Bath-Hextall, F., Delamere, F.M., & Williams, H.C. 2009. Dietary exclusions for improving established atopic eczema in adults and children: systematic review. [Review] [28 refs]. *Allergy*, 64, (2) 258-264

Bieber, T. 1962. Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.03% in children and adolescents with an acute flare of severe atopic dermatitis. *Allergy.* (2)

Boyle, R.J., Bath-Hextall, F.J., Leonardi-Bee, J., Murrell, D.F., & Tang, M.L. 2009. Probiotics for treating eczema [Systematic Review]. *Cochrane Database of Systematic Reviews* (1)

Brothers S, A.M.J. 2009. Effect of a *Mycobacterium vaccae* derivative on paediatric atopic dermatitis: a randomized, controlled trial. *Clinical and experimental dermatology.* (7)

Chamlin, S.L., Lai, J.S., Cella, D., Frieden, I.J., Williams, M.L., Mancini, A.J., & Chren, M.M. 2007. Childhood Atopic Dermatitis Impact Scale: reliability, discriminative and concurrent validity, and responsiveness. *Archives of Dermatology*, 143, (6) 768-772

CG57: Eczema, review proposal consultation document

Chen, S.-L., Yan, J., & Wang, F.-S. 2010. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: A meta-analysis of randomized clinical trials. *Journal of Dermatological Treatment*, 21, (3) 144-156

Chida, Y., Steptoe, A., Hirakawa, N., Sudo, N., & Kubo, C. 2007. The effects of psychological intervention on atopic dermatitis. A systematic review and meta-analysis. [Review] [45 refs]. *International Archives of Allergy & Immunology*, 144, (1) 1-9

Cukrowska, B., Ceregra, A., Klewicka, E., Slizewska, K., Motyl, I., & Libudzisz, Z. 2010. Probiotic lactobacillus casei and lactobacillus paracasei strains in treatment of food allergy in children. [Polish] OT - Probiotyczne szczepy lactobacillus casei i lactobacillus paracasei w leczeniu alergii pokarmowej u dzieci. *Przegląd Pediatryczny*, 40, (1) 21-25

Doss, N. 2010. Efficacy of tacrolimus 0.03% ointment as second-line treatment for children with moderate-to-severe atopic dermatitis: evidence from a randomized, double-blind non-inferiority trial vs. fluticasone 0.005% ointment. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. (2 Pt 1)

Ersser, S.J., Latter, S., Sibley, A., Satherley, P.A., & Welbourne, S. 2010. Psychological and educational interventions for atopic eczema in children [Systematic Review]. *Cochrane Database of Systematic Reviews* (2)

Fowler, J. 2007. Improvement in pruritus in children with atopic dermatitis using pimecrolimus cream 1%. *Cutis; cutaneous medicine for the practitioner*, 79, (1) 65-72

Gerasimov, S.V., Vasjuta, V.V., Myhovych, O.O., & Bondarchuk, L.I. 2010. Probiotic supplement reduces atopic dermatitis in preschool children: a

randomized, double-blind, placebo-controlled, clinical trial. American Journal of Clinical Dermatology, 11, (5) 351-361

Glazenburg EJ, W.A. 2009. Efficacy and safety of fluticasone propionate 0.005% ointment in the long-term maintenance treatment of children with atopic dermatitis: differences between boys and girls? Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. (1)

Gradman, J. 2007. Short-term growth in children with eczema during treatment with topical mometasone furoate and tacrolimus. Acta paediatrica (Oslo, Norway : 2007) 96, (8) 1233-1237

Hoeger PH, L.K.J. 160. The treatment of facial atopic dermatitis in children who are intolerant of, or dependent on, topical corticosteroids: a randomized, controlled clinical trial. The British journal of dermatology. (2)

Hon KL, 2007. Efficacy and tolerability of a Chinese herbal medicine concoction for treatment of atopic dermatitis: a randomized, double-blind, placebo-controlled study. The British journal of dermatology. (2)

Korting, H.C., Schollmann, C., Cholcha, W., & Wolff, L. 2010. Efficacy and tolerability of pale sulfonated shale oil cream 4% in the treatment of mild to moderate atopic eczema in children: A multicentre, randomized vehicle-controlled trial. Journal of the European Academy of Dermatology and Venereology, 24, (10) 1176-1182

Kupfer, J. 1968. Structured education program improves the coping with atopic dermatitis in children and their parents-a multicenter, randomized controlled trial. Journal of psychosomatic research. (4)

Langley, R.G.B., Eichenfield, L.F., Lucky, A.W., Boguniewicz, M., Barbier, N., & Cherill, R. 2008. Sustained efficacy and safety of pimecrolimus cream 1%

CG57: Eczema, review proposal consultation document

when used long-term (up to 26 weeks) to treat children with atopic dermatitis. *Pediatric dermatology*, 25, (3) 301-307

Matheson, R. 2007. Hydrocortisone butyrate 0.1% lotion in the treatment of atopic dermatitis in pediatric subjects. *Journal of drugs in dermatology : JDD*. (3)

Meurer, M., Eichenfield, L.F., Ho, V., Potter, P.C., Werfel, T., & Hultsch, T. 2010. Addition of pimecrolimus cream 1% to a topical corticosteroid treatment regimen in paediatric patients with severe atopic dermatitis: A randomized, double-blind trial. *Journal of Dermatological Treatment*, 21, (3) 157-166

Michail, S.K., Stolfi, A., Johnson, T., & Onady, G.M. 2008. Efficacy of probiotics in the treatment of pediatric atopic dermatitis: a meta-analysis of randomized controlled trials. *Annals of Allergy, Asthma, & Immunology*, 101, (5) 508-516

Paller AS, 2008. Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. *Pediatrics*. (6)

Patrizi, A. 2008 A double-blind, randomized, vehicle-controlled clinical study to evaluate the efficacy and safety of MAS063DP (ATOPICLAIR) in the management of atopic dermatitis in paediatric patients. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. (7)

Peserico, A. 2008 Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study. *The British journal of dermatology*.

Schmitt, J., Meurer, M., Schwanebeck, U., Grahlert, X., & Schakel, K. 2008. Treatment following an evidence-based algorithm versus individualised

symptom-oriented treatment for atopic eczema. A randomised controlled trial. *Dermatology*, 217, (4) 299-308

Schuttelaar ML, V.K.D. 2010 A randomized controlled trial in children with eczema: nurse practitioner vs. dermatologist. *The British journal of dermatology*. (1)

Sigurgeirsson, B. 2008. Effectiveness and safety of a prevention-of-flare-progression strategy with pimecrolimus cream 1% in the management of paediatric atopic dermatitis. *Journal of the European Academy of Dermatology and Venereology : JEADV*. (11)

Staab D, Diepgen TL, Fartasch M et al. (2006) Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: Multicentre, randomised controlled trial. *British Medical Journal* 332: 933-6.

Sugarman, J.L., Parish, L.C. 2009. Efficacy of a lipid-based barrier repair formulation in moderate-to-severe pediatric atopic dermatitis. *Journal of Drugs in Dermatology: JDD*, 8, (12) 1106-1111

Szczepanowska, J. 2008 Emollients improve treatment results with topical corticosteroids in childhood atopic dermatitis: a randomized comparative study. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. (7)

Tan, W.P., Suresh, S., Tey, H.L., Chiam, L.Y., & Goon, A.T. 2010. A randomized double-blind controlled trial to compare a triclosan-containing emollient with vehicle for the treatment of atopic dermatitis: *Clinical dermatology* * Concise report. *Clinical and Experimental Dermatology*, 35, (4) e109-e112

Thaci, D., Chambers, C., Sidhu, M., Dorsch, B., Ehlken, B., & Fuchs, S. 2010. Twice-weekly treatment with tacrolimus 0.03% ointment in children with atopic CG57: Eczema, review proposal consultation document

dermatitis: Clinical efficacy and economic impact over 12 months. *Journal of the European Academy of Dermatology and Venereology* , 24, (9) 1040-1046

Tripodi S, D.R.B. 2009. Lack of efficacy of topical furfuryl palmitate in pediatric atopic dermatitis: a randomized double-blind study. *Journal of investigational allergology & clinical immunology : official organ of the International Association of Asthmology (INTERASMA) and Sociedad Latinoamericana de Alergia e Inmunologia*. (3)

van der Aa, L.B., Heymans, H.S., van Aalderen, W.M., Sillevius Smitt, J.H., Knol, J., Ben, A.K., Goossens, D.A., Sprikkelman, A.B., & Synbad Study Group 2010. Effect of a new synbiotic mixture on atopic dermatitis in infants: a randomized-controlled trial. *Clinical & Experimental Allergy* , 40, (5) 795-804

Weber MB, Fontes Neto PT, Prati C et al. (2008) Improvement of pruritus and quality of life of children with atopic dermatitis and their families after joining support groups. *Journal of the European Academy of Dermatology & Venereology* 22: 992-7.

Woo, S.I., Kim, J.Y., Lee, Y.J., Kim, N.S., & Hahn, Y.S. 2010. Effect of *Lactobacillus sakei* supplementation in children with atopic eczema-dermatitis syndrome. *Annals of Allergy, Asthma, & Immunology*, 104, (4) 343-348

Zuberbier, T. 2007. Steroid-sparing effect of pimecrolimus cream 1% in children with severe atopic dermatitis. *Dermatology (Basel, Switzerland)*, 215, (4) 325-330

GDG References

Cork MJ, Timmins J, Holden C et al. 2003 An audit of adverse drug reactions to aqueous cream in children with atopic eczema *Pharmaceutical Journal* 271(7277), 747-748.

CG57: Eczema, review proposal consultation document

Thomas KS, 2008 A multicentre randomized controlled trial of ion-exchange water softeners for the treatment of eczema in children: protocol for the Softened Water Eczema Trial (SWET) (ISRCTN: 71423189). *The British journal of dermatology*. (3)

Tsang, M. and Guy, R. (2010), Effect of Aqueous Cream BP on human stratum corneum in vivo. *British Journal of Dermatology*, 163: 954–958