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

Atopic eczema in children

management of atopic eczema in children from birth up to the age of 12 years

Clinical Guideline

December 2007

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Commissioned by the National Institute for Health and Clinical Excellence

Evidence tables

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Evidence tables should be read in conjunction with the main guideline.

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Contents

Abbreviations

ACTH	adrenocorticotrophic hormone
ADAM	Assessment Measure for Atopic Dermatitis
ADASI	Atopic Dermatitis Area and Severity Index
ADFIS	Atopic Dermatitis Family Impact Scale
ADSI	Atopic Dermatitis Severity Index
AE	atopic eczema
APT	atopy patch test
BCSS	Basic Clinical Scoring System
BNFC	British National Formulary for Children
BSA	body surface area
CADIS	Childhood Atopic Dermatitis Impact Scale
CBCL	Child Behaviour Checklist
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
CIPQ	Children's Illness Perception Questionnaire
CLQI	Children's Life Quality Index
Costa's SSS	Costa's Simple Scoring System
CPMS	Childhood Psychopathology Measurement Schedule
DB	double-blind
DBPCFC	double-blind placebo-controlled food challenge
DFI	Dermatitis Family Impact scale
DS	diagnostic study
EASI	Eczema Area and Severity Index
EL	evidence level (level of evidence)
EPO	evening primrose oil
FEN	*Fragebogen zur Lebenqualität von Eltern neurdermitiskranker Kinder* (German quality of life questionnaire for parents of children with atopic dermatitis)
FES	Family Environment Scale
FP	fluticasone propionate
g	gram
GDG	Guideline Development Group
GHQ	General Health Questionnaire
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HC	hydrocortisone
HPA	hypothalamic–pituitary–adrenal
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IDQoL	Infants' Dermatitis Quality of Life index
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IQR	interquartile range
ISAAC	International Study of Asthma and Allergies in Childhood
ISOLATE	International Study of Life with Atopic Eczema
JUCKJU	an itching scale
JUCKKI	an itching scale
KINDL	a generic quality of life questionnaire in German for children and adolescents
KITA	a generic quality of life questionnaire in German for children aged 0–6
l	litre
MHRA	Medicines and Healthcare products Regulatory Agency
µg	microgram

ml	millilitre
n	number of patients
N/A	not applicable
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NESS	Nottingham Eczema Severity Score
ng	nanogram
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPV	negative predictive value
NS	not statistically significant
NSAI	nonsteroidal anti-inflammatory
OR	odds ratio
OSAAD	Objective Severity Assessment of Atopic Dermatitis
PCT	primary care trust
PIQoL-AD	Parents' Index of Quality of Life in Atopic Dermatitis
POEM	Patient-Oriented Eczema Measure
PPIP	Patient and Public Involvement Programme
PPV	positive predictive value
PQoL-AD	Quality of Life in Parents of Children with Atopic Dermatitis
PRIST	paper radioimmunosorbent test
PRU	pruritus severity
PTI	Personality Trait Inventory
QALY	quality-adjusted life year
QOL	quality of life
r	correlation coefficient
RAST	radioallergosorbent test
RCT	randomised controlled trial
RR	relative risk
SA	Subject's Assessment
SA-EASI	Self-Administered Eczema Area and Severity Index
SAFT	skin application food test
SA-NESS	Self-Administered Nottingham Eczema Severity Score
SASSAD	Six Area, Six Sign, Atopic Dermatitis score
SCORAD	Scoring Atopic Dermatitis index
SD	standard deviation
SDS	standard deviation score
SE	standard error
SF-36	Short Form 36
SIGN	Scottish Intercollegiate Guidelines Network
SIS	skin intensity score
SPT	skin prick test
SQ	Symptom Questionnaire
STAI	state trait anxiety index
TA	technology appraisal
TBSA	total body severity assessment
TCS	topical corticosteroid
TIS	Three Item Severity score
URTI	upper respiratory tract infection
VAS	visual analogue scale

Diagnosis

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
Williams HC;Burney PG;Hay RJ;Archer CB;Shipley MJ;Hunter JJ;Bingham EA;Finlay AY;Pembroke AC;Graham-Brown RA; 1994 Sep [27]	Derivation of a minimum set of discriminators for atopic eczema. EL=2+/DS II	Intervention: Diagnostic criteria vs clinical diagnosis of atopic eczema Comparison: Observations made by two observers (dermatology registrars or senior registrars) using 31 of the Hanifin and Rajka criteria, compared with the diagnosis made by a physician with an interest in dermatology.	224 (120 cases, 104 controls)	Consecutive new cases of 'typical mild to moderate atopic eczema' (aged 6 months to 50 years), and 2 control groups: patients with an inflammatory skin disorder other than atopic eczema, and a community control group with no overt skin disease. 53% of cases were aged <10 yrs. 102 participants (46%; 70 cases, 32 controls) were aged <16 yrs. Ethnicity: 82% White, 5% Indian subcontinent, 9% Afro-Caribbean, 3% Oriental, 1% 'other'. Cases were significantly younger than controls (p<0.01), and non-whites were significantly underrepresented in the control group, p=0.01.	Discriminatory value of diagnostic criteria	Of the 31 criteria, 15 were eliminated because of having chi square value <10, or poor interobserver reliability (kappa scores <0.4). Of the 16 remaining criteria, subjected to regression analysis, the regression equation for the log odds of atopic eczema = -5.6+2.4 history of flexural dermatitis +3.7 onset under 2 +1.2 presence of itchy rash +1.9 personal history of asthma +1.3 history of a dry skin +1.3 visible flexural dermatitis. Although history of itchy skin became insignificant when visible flexural dermatitis was added to the final model, it was retained because pruritus was felt to be an essential feature of atopic eczema. In children aged <16 yrs, the regression equation was: = -4.36+1.84 history of flexural dermatitis +3.46 onset under 2 +2.09 visible flexural dermatitis + 1.71 presence of itchy rash	Funding: Stiefel UK sponsored the first meeting of the working party. Lead author was supported by a fellowship from the Wellcome Trust. The observers were unaware of the true purpose of the study; observers' responses were concealed from physicians at all times, and observers were also blind to the physician's diagnosis. Sixteen physicians were involved in the study, 13 of whom had a special interest in atopic eczema, and 6 were paediatric dermatologists. The population included were consecutive new cases of 'typical mild to moderate atopic eczema' (aged 6 months to 50 years), and a control group of patients with an inflammatory skin disorder other than atopic eczema. Exploratory analysis was undertaken to assess whether the 6 criteria were influenced by ethnic class - there was 'no evidence' of a difference, but no data were presented.

Bibliographic information	Study type and evidence level	Number of patients and prevalence	Population characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Williams HC, Burney PGJ, Pembroke AC et al 1994 [28]	Validation study of the UK Working Party criteria in hospital outpatients. EL=DS II	114 (39 cases, 75 controls)	Dermatology outpatients (27% were children aged 10 yrs or under), and paediatric outpatients, aged up to 16 yrs. Paediatric outpatients: 51% female, median age cases 5 yrs (IQR 2-10), vs. 6 yrs controls (IQR 3-9). 51% White, 27% Afro-Caribbean, 11% Indian subcontinent, 11% Chinese/Middle-Eastern/mixed. Control groups had other conditions such as inflammatory dermatoses, or infections.	Test: Diagnostic validity of the UK working Party criteria. Reference standard: Diagnosis using the proposed composite criteria (itchy skin as a major criterion, with three or more of the other five) compared with a dermatologist's diagnosis	Optimum discrimination given by itch plus 3 or more criteria (sensitivity 85%, 95% CI 69 to 94%; specificity 96%, 95% CI 89 to 99%) PPV and NPV both 92%. Data for each composite criterion evaluated: Itch plus 2 criteria: sens 92%, spec 81%, RV 73.6 Itch plus 3 criteria: sens 85%, spec 96%, RV 80.6 Itch plus 4 criteria: sens 54%, spec 99%, RV 52.5% Itch plus minus asthma/hay fever: sens 72%, spec 97%, RV 69.1 Itch plus 2 minus signs: sens 85%, spec 87%, RV 71.3 Itch plus 2 minus signs and asthma/hay fever: sens 75%, spec 89%, RV 63.7 Omitting asthma/hay fever resulted in a reduced sensitivity and increased specificity, and omitting the sign of visible flexural dermatitis resulted in a fall in specificity from 96% to 87%. Addition of xerosis or hypopigmented patches did not results in an improvement in discrimination.	Funding: none declared. While the dermatology outpatients study included some data for children within the age group of interest to this guideline, no demographic data were provided therefore that part of the study is not considered further. Some questions were modified after the dermatology outpatients validation study; in younger children the criteria age of onset under 2 years, and personal history of hay fever may not be applicable, therefore for children aged under 4 years, the criterion onset under 2 years was not used, and history of asthma/hay fever was replaced with history of atopic disease in a first degree relative. In addition, because distribution of eczema may be different in young children, visible dermatitis on the cheeks and/or the outer aspects of the limbs were included as part of 'visible flexural dermatitis' in children aged under 4 years, and 'history of flexural dermatitis' included dermatitis on the cheeks in children under 10 years. Sensitivity and specificity in Afro-Caribbean subgroup considered to be comparable to the total group (sens 11/14, spec 17/17) 'Relative value' was also quoted in the paper (sensitivity plus specificity minus 100) – data not reproduced here.

Bibliographic information	Study type and evidence level	Number of patients and prevalence	Population characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Williams HC;Burney PGJ;Pembroke AC;Hay RJ; 1996 [30]	Validation of diagnostic criteria (diagnostic accuracy), EL=DS II	n=695 Prevalence 8.5%	School children aged 3 to 11 yrs (31% aged 3-5.9, 38% aged 6-8.9, 31% aged 9-11); mean age 7 (SD 2.4). Ethnic grps: 43% White, 8% Indian subcontinent, 32% Black, 15% Mixed, 2% other. 49% male, 51% female.	Test: Diagnosis of atopic eczema in schoolchildren using the UK diagnostic criteria Reference standard: clinical diagnosis by a paediatric dermatologist	Itchy skin condition: sens 86%, spec 77%, PPV 26%, NPV 98%. Onset under age 2 yrs: sens 47%, spec 94%, PPV 45%, NPV 95%. History of flexural rash: sens 76%, spec 89%, PPV 39%, NPV 98%. History of asthma or hay fever: sens 56%, spec 70%, PPV 15%, NPV 94%. History of dry skin: sens 85%, spec 71%, PPV 21%, NPV 98%. Visible flexural dermatitis: sens 63%, spec 95%, PPV 54%, NPV 96%. Composite criteria under test: itch plus 3 or more: sens 70%, spec 93%, PPV 47%, NPV 97% Criteria adjusted for 1-yr period prevalence (adjusted for cases that were deemed by a physician to have had AE in the last year): itch plus 3 or more: sens 80%, spec 97%, PPV 80%, NPV 97%. Sensitivity and specificity of the UK Working Party diagnostic criteria for atopic eczema, relative to a clinical diagnosis by a paediatric dermatologist.	Funding: none declared, but lead author funded by the Wellcome Trust when the work was carried out. Parents completed a questionnaire requesting background information, plus the 5 questions of the UK working party criteria (response rate 75%). Self-reported skin disease was also recorded. Reference point for diagnosis of eczema was the clinical diagnosis by a dermatologist with an interest in paediatric dermatology, but unaware of the results of the questionnaire or of the diagnostic criteria. Dermatologist also assessed severity (very mild <5% involvement, justifies emollient; mild <5% involvement but requiring 1% hydrocortisone? in addition to emollients; moderate 5-30% involvement requiring moderate-potent topical corticosteroids; severe >30% involvement needing specialist supervision). A nurse independently assessed whether the criterion visible flexural dermatitis was present. Point prevalence of atopic eczema (dermatologist diagnosis) was 8.5% Repeatability of questionnaire also assessed in 73 cases; Kappa agreement above 0.85, and 'mean pair agreement indexes' 0.93. Validity of the criteria in certain subgroups were also explored (incl age and ethnicity), although results only given for under 4 yrs, and according to severity.

Bibliographic information	Study type and evidence level	Number of patients and prevalence	Population characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Popescu CM;Popescu R;Williams H;Forsea D; 1998 Mar [31]	Validation of diagnostic criteria (diagnostic accuracy), EL=DS II	1114	Children aged 6 to 12 years from 3 schools in Bucharest. Mean age 9yrs (SD 1.2). 54% male. 98% White Romanian, 1% Gypsy, 1% Mixed, 0.1% others.	Test: UK Working party diagnostic criteria, administered by questionnaire completed by parents/children/school teachers Reference standard: Clinical diagnosis of a dermatologist with an interest in eczema	Itchy skin condition: sens 78%, spec 94%, PPV 24%, NPV 99%. Onset under age 2 yrs: sens 37%, spec 97%, PPV 21%, NPV 98%. History of flexural rash: sens 74%, spec 96%, PPV 32%, NPV 99%. History of asthma and/or hay fever: sens 44%, spec 90%, PPV 10%, NPV 99%. History of dry skin: sens 67%, spec 83%, PPV 91%, NPV 99%. Visible flexural dermatitis: sens 59%, spec 98%, PPV 40%, NPV 99%. Composite criteria under test: itch plus 3 or more: sens 74%, spec 99%, PPV 63%, NPV 99% Diagnostic accuracy of the UK working party criteria compared with clinical diagnosis as reference standard	Funding: Sir Samuel Scott of Yews Trust. Parents/children/class teachers completed a questionnaire covering the UK working party criteria (response rate 88%). Self-reported skin disease was also recorded. Reference point for diagnosis of eczema was the clinical diagnosis by a dermatologist with an interest in eczema, but unaware of the results of the questionnaire or of the diagnostic criteria. Dermatologist also assessed severity (very mild <5% involvement, justifies emollient; mild <5% involvement but requiring 1% hydrocortisone in addition to emollients; moderate 5-30% involvement requiring moderate-potent topical corticosteroids; severe >30% involvement needing specialist supervision). A nurse independently assessed whether the criterion visible flexural dermatitis) was present. Point prevalence of atopic eczema (dermatologist diagnosis) was 2.4% Repeatability of questionnaire also assessed in 171 cases; Kappa agreement above 0.72, and 'mean pair agreement indexes' 0.92. Validity of the criteria in certain subgroups were also explored (incl age and ethnicity), although results only given for under 4 yrs, and according to severity.

Bibliographic information	Study type and evidence level	Number of patients and prevalence	Population characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Chalmers DA;Todd G;Saxe N;Milne JT;Tolosana S;Ngcelwane PN;Hlaba BN;Mngomeni LN;Nonxuba TG;Williams HC; 2007 [32]	Validation of diagnostic criteria (diagnostic accuracy), EL=DS III	3067 Point prevalenc: 1.04 (95% CI 0.6-1.4)	Black Xhosa speaking children aged 3-11 years, mean age 6.6 (s.d. 2.5), 52.4% female, 33% urban, 33% peri-urban, 34% rural	Test: Validity of the UK Working Party diagnostic criteria for atopic eczema in a Xhosa-speaking African population. Reference standard: Clinical diagnosis by one of three dermatologists .	Percentage (95% CI) Q1a) Itchy skin in last year: sens 71.8 (53.2, 86.2), spec 49.2 (47.4, 51.0), ppv 1.4 (0.9, 2.2) npv 99.4 (98.8, 99.7) Q1b) Itchy skin in last week: sens 68.7 (49.9, 83.8), spec 51.6 (49.8, 53.4) ppv 1.4 (0.9, 2.2) npv 99.3 (98.8, 99.7 Q2) Onset of this skin condition under 2 years: sens 9.3 (1.9, 25.0), spec 97.5 (96.9, 98.0), ppv 3.9 (0.8, 10.9), npv 99.0 (98.6, 99.3) Q3) History of this skin condition ever affecting the skin creases: sens 68.7 (49.9, 83.8), spec 68.8 (61.1, 64.5), ppv 3.4 (2.1, 5.2), npv 99.5 (99.1, 99.7) Q4) History of generally dry skin in the last year: sens 62.5 (43.6, 78.9), spec 81.5 (80.1, 82.9), ppv 3.4 (2.1, 5.2), npv 99.5 (99.1, 99.7) Q5a) Personal history of hay fever: sens 6.2 (0.7, 20.8), spec 97.1 (96.4, 97.6), ppv 2.2 (0.2, 7.8), npv 98.9 (98.5, 99.3) Q5b) Family history of asthma, hay fever or eczema for children under 4 years: sens 0.0 (0.0, 10.6), spec 98.8 (98.4, 99.2), ppv 0.0 (0.0, 10.0), npv 98.9 (98.5, 99.2) Q6) Visible flexural eczema:	Questionnaires were translated, validated in a pilot study and administered by bilingual interviewers. No inter-observer variability study was reported for diagnosis by a dermatologist. The UK working party criteria for diagnosing atopic eczema do not work well in a Xhosa-speaking population of children. The single visible of sign of visible flexural eczema works well alone as a diagnosing factor.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Fleming S;Bodner C;Devereux G;Russell G;Campbell D;Godden D;Seaton A; 2001 Dec [33]	Study Type: Case-control Evidence level: 2+	Nested case-control study from a survey of 2000 mothers, on the 1st birthday of their infants (81% response rate). 118 cases/controls selected, of which 108 (53/59 cases, and 55/59 controls) took part.	Cases were those with the diagnosis of atopic eczema based on the results of the mailed questionnaire. Controls had never had an itchy skin condition or they had an itchy skin condition but no more than 2 of the additional criteria (of the UK Working Party criteria). 43% of infants were male, 57% female. Overall 75% had family history of atopy. Cases (vs. controls) were more likely to have a positive family history of atopy, have a doctor's diagnosis of eczema, and to be using medications for eczema, p<0.001 for each.	Intervention: Mother's diagnosis of atopic eczema based on self-completion of questionnaire listing the UK Working Party criteria. Comparison: Nurse's diagnosis by face-to face interview (using same questions as used in the questionnaire).	Follow-up period: N/A Outcome Measures: Agreement between mother's and nurse's diagnosis - for each criterion, and for the diagnosis of atopic eczema (based on itch plus 3 or more criteria, and based on itch plus all criteria)	% agreement (Kappa score, 95% CI) for each criterion in cases and controls: itchy skin 97.2% (k=0.94, 0.84 to >1) history of flexural rash 95.4% (k=0.91, 0.78 to >1) family history 94.4% (k=0.89, 0.75 to >1) history of dry skin 88.9% (k=0.75, 0.56 to 0.94) visible dermatitis today 89.8% (k=0.78, 0.60 to 0.96) Diagnosis of eczema using itch plus 3 or more UK criteria 96.3% (k=0.93, 0.81 to >1) Diagnosis of eczema using itch plus all UK criteria 94.4% (k=0.89, 0.75 to >1)	Funding: National Asthma Campaign. Infants included in the study were more likely to have fathers in a nonmanual social class, and have mothers who were never smokers compared with the remaining cohort.

Assessment of severity, psychological and psychosocial wellbeing and quality of life

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Charman C;Williams H; 2000 Jun [39]	Study Type: Systematic review - meta-analysis Evidence level: II	-	Adults and Children	Intervention: Measures of disease severity ADAM ADASI ADSI BCSS Costa's SSS EASI Leicester NESS Rajka and Langeland SASSAS SCORAD SIS TBSA Patient global severity score Observer global severity score Quality of life score Individual components of scores Comparison: Any	Follow-up period: range Outcome Measures: Validity - Content, Construct, Criterion Reliability - Interobserver reliability, Intraobserver reliability, Internal consistency Responsiveness - Sensitivity to change Acceptability - Time to administer	13 atopic eczema scales identified (ADAM, ADASI, ADSI, BCSS, Costa's SSS, EASI, Leicester, NESS, Rajka and Langeland, SASSAS, SCORAD, SIS, TBSA). The results validity (content, construct, criterion), reliability (interobserver reliability, intraobserver reliability, internal consistency) responsiveness (sensitivity to change) and acceptability (time to administer) were reported where available, but not compared. 10 scales had data on construct or criterion: ADAM, BCSS, Costa's SSS, Leicester, NESS, Rajka and Langeland, SASSAS, SCORAD, SIS, TBSA) 5 scales had been tested for reliability (interobserver variability, intraobserver variability, or internal consistency): ADAM, BCSS, Costa's SSS, EASI, SCORAD Data on responsiveness to change was available on 8 scales (ADASI, ADSI, BCSS, Costa's SSS, SASSAS, SCORAD, SIS, TBSA) An estimated time to administer the	To test validity and reliability of the severity scale various attributes of the results need to be tested and the results assessed. The systematic review identified which scores had been tested for various attributes but did not compare the results. There are a number of different ways of testing validity, reliability, responsiveness to change and acceptability. No clinical outcomes are reported comparing the use of different scales. No objective measure is given for the results of the statistical analysis. Different statistical tests were used to calculate the agreement for different comparisons. The results from different statistical tests are difficult to compare. Further studies have been published since this systematic review.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
				comparison identified in search was reported, no further analysis was performed		measure had been given for 3 scales (ADASI, SASSAD, SCORAD)	
Johnke H; 2006 147	Study Type: Cohort Evidence level: 2-	553 61 had AE	Infants born at term recruited to study. Followed up at 3, 6, 9, 12 and 18 months	Intervention: Association between high level, transient and persistent sensitization and development of AE. Comparison: Any allergen versus none as measured by histamine release, sIgE and SPT Transiently and persistently sensitised to any allergen versus never as measured by histamine release, sIgE and SPT	Follow-up period: 3, 6, 9, 12 and 18 months of age Outcome Measures: Odds ratios for atopic eczema. Predicting factors more than one allergen or type of sensitivity. Two classifications of allergy are defined. Class 1 where SPT wheal size is >= 2mm and Class 2 where SPT wheal is >= 3mm Class 2 results are reported.	Outcome: atopic dermatitis Predictor: more than one allergen vs none Histamine release OR 2.74 (CI 1.11-6.27) sIgE OR 3.56 (CI 1.83-6.75) SPT OR7.57 (CI 3.33-16.71) Predictor: transiently sensitised vs never Histamine release OR 1.98 (CI 0.43-7.32) sIgE OR 1.81 (CI 0.70-4.48) SPT OR 6.93 (CI 2.32-19.28) Predictor: persistently sensitised vs never Histamine release OR 1.98 (CI 0.32-8.76) sIgE OR 6.25 (CI 2.17-17.33) SPT OR 12.67 (CI 4.03-39.72)	AE is associated with persistent sensitisation but not with transient association at age 18 months. Confidence intervals for persistant sensitisation are very wide so results not credible.s.
Charman C;Chambers C;Williams H; 2003 Jun 40	Study Type: Systematic review - meta-analysis Evidence level: 3		Adults and Children	Intervention: Systematic review to identify how the severity of atopic eczema was measured in RCTs between 1994-2001. Comparison:	Follow-up period: Outcome Measures: Frequency of use of each scale which components were in the scale	93 RCTs identified 85 RCTs (91%) reported using an objective measurement of clinical signs 23 RCTs (27%) used a published severity scale 12 RCTs (14%) used modified versions of published scales 50 RCTs (59%) used unnamed scales with no data on validity or reliability	Studies in adults and children included

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						31 different descriptions of clinical signs being used across all scoring systems. 56 different "objective" clinical scales were identified 80 trials (86%) patients symptoms were reported 62 trial (67%) disease extent was reported Other outcome measures 3 trials measured quality of life 15 trial recorded topical steroid requirements 4 trials recorded antihistamine use SCORAD (15 trials), EASI (4 trials), SASSAD (4 trials) and Costa's SSS (4 trials) were the most used scales.	

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
Pucci N;Novembre E;Cammarata MG;Bernardini R;Monaco MG;Calogero C;Vierucci A; 2005 Jan [70]	Study Type: Other Evidence Level: II	Intervention: SCORAD	63	Children with atopic eczema, mean age (±SD) 17.5 ± 11.15 months (range 2-48 months)	Comparison of different parameters and the total SCORAD index using Student's t-tests and Pearson's correlation coefficient.	There was a positive correlation between three parameters of the SCORAD index (numbers not given). Total SCORAD was strongly correlated with each item: extent ($p<0.0001$, $r = 0.79$), intensity ($p< 0.0001$, $r=0.91$ and subjective symptoms ($p<0.0001$, $r = 0.71$).	
Stalder JF;Taieb A;Atherton DJ;Bieber T;Bonifazi E;Broberg A;Calza A;Coleman R;de PY;Diepgen TL;Gelmetti C;Giannetti A;Harper J;Kunz B;Lachapelle JM;Langeland T;Lever R;Oranje AP;Queille-Roussel C; 1993 [53]	Study Type: Other Evidence Level: 3	Intervention: SCORAD: Inter-observer variability and intra-observer variability (for erythema, oedema, oozing, lichenification and excoriation) objective SCORAD evaluated in 10 photos		Photos of 10 people evaluated by 10 trained investigators to provide interobserver reliability data.		Intra-observer variability: 0.84, $p>0.05$ Inter-observer variability:0.92, $p<0.01$	No details were given for the patients in the photos. Study included in the systematic review [39] The development of the SCORAD scale was undertaken in this study, which involved 88 patients, aged 1 month to 60 years (mean 7 years).
Tripodi S;Panetta V;Pelosi S;Pelosi U;Boner AL; 2004 [78]	Study Type: Other Evidence Level: 3	Intervention: Extent of lesion as a percentage of involved zones estimated by 20 physicians untrained in the evaluation of the skin disease. Ist by sight only 2nd with use of computer 'ScordCard' Comparison: Exact number of pixels counted by using	2 photos of children	Colour photos of two children front and back view with artificial painted zoned representing skin lesions	Difference between percentage of area involved in lesion measured by 'sight only' estimate and 'computer evaluation' Difference between percentage of area involved in lesion measured by computer assistance with 'ScordCard' and 'computer evaluation'	Computer evaluation percentage of area involved: 38.06% Sight only 43.44% 95%CI 36.04-39.94. Difference between 'sight only' estimate and 'computer evaluation': $p = 0.002$ ScoradCard 37.99% 95%CI 36.04-39.94. Difference between computer assistance with 'ScordCard' and 'computer evaluation': $p = 0.79$	This study was carried out on only 2 photographs with computer-generated skin lesions.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
		specific photograph elaboration software (described as 'gold standard')					
Wolkerstorfer A;Laan MP;Savelkoul HF;Neijens HJ;Mulder PG;Oudesluys-Murphy AM;Sukhai RN;Oranje AP; 1998 Mar 531	Study Type: Other Evidence Level: 3	Intervention: Measure of soluble E-selectin, serum eosinophil cationic protein, soluble intracellular adhesion molecule-1, soluble vascular cell adhesion molecule-1 and soluble P-selectin and SCORAD.	40	Children aged 13- 36 months, mean age 22.3 months, mainly with mild to moderate atopic eczema.		Correlation between soluble E-selectin and SCORAD, rs=0.6013, p < 0.05 No correlation between serum eosinophil cationic protein and SCORAD, rs=0.254, p = 0.15 No correlation between soluble intracellular adhesion molecule-1, soluble vascular cell adhesion molecule-1 and soluble P-selectin	There is no objective measure for the results of the statistical analysis Soluble E-selectin, serum eosinophil cationic protein, soluble intracellular adhesion molecule-1, soluble vascular cell adhesion molecule-1 and soluble P-selectin are not measured in clinical practice.
Balkrishnan R;Housman TS;Carroll C;Feldman SR;Fleischer AB; 2003 May 60	Study Type: Other Evidence Level: II	Intervention: SA-EASI ADFIS (Atopic Dermatitis Family Impact Scale - a slightly modified version of the Dermatitis Family Impact (DFI)) Comparison:	49	Children (mean (±SD) = 4.7 (± 3.4) (range 6 months to 12 years) with atopic eczema, unknown inclusion and exclusion criteria	Validity - construct Correlation between SA-EASI and ADFIS, using a paired t-test, and multiple regression analysis Correlation between parent perception of severity and SA-EASI score	Validity - construct Correlation between SA-EASI and ADFIS (p = 0.62, p < 0.001 at baseline and p = 0.38, p<0.05 at follow up) Correlation between parent perception of severity and SA-EASI score (r = 0.45, p< 0.01 at baseline 'week to moderate', r = 0.12, p > 0.05 at follow up - no correlation	There is no objective measure for the results of the statistical analysis.
Ben-Gashir MA;Seed PT;Hay RJ; 2002 Sep 74	Study Type: Other Evidence Level: II	Intervention: SCORAD DFI (Dermatitis Family Impact)	116	Mean age 8 years (range 5-10 years) with atopic eczema identified by general practitioners.	Validity - construct Objective SCORAD compared to the quality of life measured by the Dermatitis Family Impact questionnaire (DFI).	Validity - construct Objective SCORAD correlated with DFI (regression coefficient = 0.17(95%CI 0.06-0.29, p = 0.002).	There is no objective measure for the results of the statistical analysis.
Ben-Gashir MA;Seed PT;Hay RJ; 2004 Feb 75	Study Type: Other Evidence Level: II	Intervention: Objective SCORAD and CDLQI completed by the child	116	Mean age 8 years (range 5-10 years) with atopic eczema identified by general practitioners Children also studied in 74	Validity - construct Objective SCORAD compared to the Children's Dermatology Life Quality Index (CDLQI), using Spearman correlation coefficient and multiple	Validity - construct Objective SCORAD compared to the Children's Dermatology Life Quality Index (CDLQI): at first visit r = 0.52, p < 0.001 and after 6 months r = 0.59, p < 0.001. This remained significant even after controlling for potential	

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					regression.	confounders.	
Ben-Gashir MA;Hay RJ; 2002 Nov 80	Study Type: Other Evidence Level: II	Intervention: SCORAD	137	82 urban (42 white children and 26 black children and 14 from other races) and 55 rural (55 white children) were recruited.	Difference in severity of disease (measured by SCORAD) between white and black children, unadjusted and adjusted for erythema.	Unadjusted analysis found that black children had same severity of disease as white children (OR 0.84; 95%CI 0.4-1.76, p = 0.65) after adjusting for the erythema scores children of Black origin had more severe eczema than the white children (OR 5.93; 95%CI 1.94-18.12; P= 0.002).	
Bringhurst C;Waterston K;Schofield O;Benjamin K;Rees JL; 2004 Dec 69	Study Type: Other Evidence Level: 3	Intervention: Study of nocturnal movements using a wrist-worn accelerometer, subjective measured about the extent of skin disease, itch and quality of sleep. 20 children were studied on more than one occasion Comparison: Nocturnal activity score compared for children with atopic eczema and without atopic eczema Spearman correlation coefficient between nocturnal activity score and SCORAD, objective SCORAD and visual analogue response to questions.	25 Children with atopic eczema aged 2 to 13 years (mean age 5). 17 Children without atopic eczema aged 2 to 15 years (mean age 7)			Mean nocturnal activity score (per hour) higher for children with atopic eczema than children without eczema p< 0.001 (numbers not given) Spearman correlation coefficient between nocturnal activity score and SCORAD rho = 0.62, p = 0.003 Nocturnal activity score and objective SCORAD rho = 0.57, p = 0.007 Nocturnal activity score and visual analogue itch rho = 0.40, p = 0.049 Nocturnal activity score and visual analogue skin disease rho = 0.49, p = 0.0158	Funding: Wellcome Trust, and GlaxoSmithKline.
Charman CR;Venn AJ;Williams HC; 2002 Jun 62	Study Type: Other Evidence Level:	Intervention:	6	Children and adults aged 3-35 years with moderate to severe atopic eczema (3 were aged 12 years or under).	1) Median SASSAD scores per patient (range) 2) Interobserver variation in median scores, and intraclass correlation coefficient	1) 44 (32-53) 16.5 (10-28) 41.5 (40-53) 45.5 (33-63) 31.5 (27-38) 31.5 (26-33)	Funding: Health Services Research Training Fellowship. The observers were: 2 consultant dermatologists 1 dermatology specialist registrar

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
							3 dermatology research fellows
					3) Interobserver agreement for individual elements of the score (kappa scores, range) 4) Intraobserver variation	2) 7-30 (median 15.5); intraclass correlation coefficient 0.7 (good agreement) 3) head and neck -0.01 to 0.46 hands -0.03 to 0.48 arms 0.01 to 0.41 trunk 0.07 to 0.36 feet 0.09 to 0.36 legs 0.04 to 0.27 4) Maximum 8 out of 108	
Charman CR;Venn AJ;Williams HC; 2004 Dec [51]	Study Type: Other Evidence Level: II	Intervention: POEM patient global assessment of disease severity overall bother related to the eczema	435	Children and adults (age range 1 to 58 years, median age 17 years) with atopic eczema from out patient department.	Validity-content: content questionnaire concerning symptoms to 200 children and adults with atopic eczema. Validity-construct: POEM was correlated with CDLQI. Validity-criterion: POEM correlated against patient global assessment of disease severity (5 point scale) and overall bother relating to the eczema (10 point scale) during the 1 week period. Reliability – Intraobserver reliability: 50 Patients completed POEM twice, 24 to 48 hours apart. Sensitivity to change: New measure was completed by 40 new outpatients (age range 1-36 years, median age 4	Validity-content: A questionnaire sent to 200 children and adults with atopic eczema asked about itch, pain/soreness, sleep loss, bleeding, weeping/oozing, cracking, flaking, dry/roughness, redness and tightness of skin. The symptoms were incorporated into a scoring system that asked how frequently they were experienced in the last week. However, redness, tightness and pain/soreness were excluded because patients found them difficult to understand or assess. Validity-construct: POEM was correlated with CDLQI (n = 68, r=0.73; p<0.001) 'good' Validity-criterion: POEM correlated against patient global assessment of disease severity (n=200; r=0.81, p < 0.001) and overall bother related to the eczema (n=200, r=0.84, p< 0.001) during the 1 week period 'high correlation' Reliability – test-retest reliability:	There is no objective measure for the results of the statistical analysis. The interval between test and retest was 24-48 hours.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
					year) at 0, 1 and 4 weeks. 18 week topical corticosteroid RCT Internal consistency: 200 patients completed POEM, (aged 12 months to 69 years, medium 9 years), symptoms scores were compared using Cronbach α, a α of 0.7 to0.9 is thought to be ideal.	50 patients completed POEM twice (24 to 48 hours apart), difference between the scores = 0.04(SD = 1.32) (Bland and Altman used) Sensitivity to change: All 7 symptoms showed a mean decrease during the 4-week period 18 week topical corticosteroid RCT, all variables showed an improvement. Internal consistency: Scores showed high homogeneity or internal consistency (Cronbach α=0.88).	
Charman D;Varigos G;Horne DJ;Oberklaid F; 1999 [41]	Study Type: Other Evidence Level: 3	Intervention: ADAM each child assessed by two doctors out of 5 (3 dermatologists and 2 dermatology trainees). Value kappa greater than 70% used as a criterion for the level of significance between physicians.	51	Children aged between 5 months and 161 months (13.4years) (mean age 70 months) Included in systematic review [39]		Correlation (kappa scores) between observers, of individual components. For sites and morphological items: pruritus 0.6* face 0.45* arms 0.41* hands 0.5* legs 0.4* feet 0.47* trunk 0.13 scalp 0.78** napkin area 0.56** head/neck/flexures 0.39** legs/arms/flexures 0.64**	*p<0.1 **p<0.05 Kappa scores were pooled and not weighted. Comparison was made blind, within 30 minutes.
Charman DP;Varigos GA; 1999 [42]	Study Type: Other Evidence Level: 3	Intervention: ADAM: each child assessed by two doctors (out of 5, 3 dermatologists and 2 dermatology trainees). Global ratings of severity by dermatologist	171	Children with atopic eczema aged from 4 to 193 months (16 years) mean age 54 months (4.5 years) Included in systematic review [39]		Agreement between ADAM and physicians global rating of severity. Kappa=0.40, p<0.05. Crude agreements/disagreements: 53/42 for mild, 5/18 for severe	There is no objective measure for the results of the statistical analysis.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
Emerson RM;Charman CR;Williams HC; 2000 Feb [48]	Study Type: Other Evidence Level: II	Intervention: NESS Global severity assessed by dermatologist Severity assessment by parent Topical corticosteroids use	290	Children aged 1 to 5 years, selected from registers of four general practices.	Validity – Construct NESS correlation with global severity assessment by a dermatologist (graded as mild, moderate and severe) NESS correlation with severity assessment by parent (graded as mild, moderate and severe) NESS correlation with impairment of quality of life measured by CLQI (Children's Life Quality Index) NESS correlation with use of topical corticosteroids: Mild and moderate and potent topical corticosteroids used over the previous 12 months Time to administer	Validity – Construct NESS agreement with global severity assessment by a dermatologist: exact agreement in 88% of cases NESS agreement with severity assessment by parent: exact agreement in 75% of cases NESS correlation with impairment of quality of life measured by CLQI: Pearson's correlation coefficient = 0.224, P> 0.05 NESS correlation with use of topical corticosteroids in the previous 12 months: Mild potency topical corticosteroids were used by 62% (mild), 94% (moderate) and 100% of severe cases. Moderate or potent corticosteroids were used in 18% (mild), 36% (moderate) and 76% of severe cases. Time to administer: 'Easily completed in a few minutes'	There is no objective measure for the results for the statistical analysis.
Hanifin JM;Thurston M;Omoto M;Cherill R;Tofte SJ;Graeber M; 2001 Feb [59]	Study Type: Other Evidence Level: II	Intervention: 15 dermatologists independently evaluated the atopic eczema using EASI following 30 minutes of training	10	Age range 0 to 7 years mean (4.3 years) Children with atopic dermatitis from a specialist clinic were selected by investigator 'to achieve a broad range of disease severity and body region involvement'	Reliability Interobserver reliability: 15 dermatologists assessed EASI in patients. The results were compared using random effects model to investigate variability giving a correlation coefficient (r-hat) the proportion of overall variability explained by subject-to-subject variability. (r-hat between 0.4-0.75 = fair to good	Reliability Interobserver reliability: EASI r-hat 0.66 (lower 95%CI 0.48) on day one and 0.59 (lower 95% CI 0.4) on day two ('fair-good'). Induration/papulation was the most difficult sign to assess (had the lowest kappa score; 0.269 on day 1, 0.226 on day 2; kappa scores for other parameters were in the range of 0.383-0.496) Intraobserver variability: EASI	Interobserver variability for each of the clinical signs (erythema, infiltration/papulation, excoriations, lichenification) was assessed separately, but the results were only reported for a combined group of children and adults (n=10).

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					reliability, > 0.75 excellent reliability) Intraobserver variability: EASI, retest interval 1 day, scores on two days were compared using simple linear regression analysis and mixed effects model	regression coefficient 0.66. Mixed effects model showed some evidence of significant effect of the day (p = 0.042)	
Hon KL;Ma KC;Wong E;Leung TF;Wong Y;Fok TF; 2003 Nov [49]	Study Type: Other Evidence Level: II	Intervention: NESS SCORAD Comparison: Validity - Criterion: Physicians assessment with NESS score compared to physician assessment with SCORAD score using a Bland and Altman plot. Accompanying parent's or child's own assessment of atopic dermatitis with NESS score translated into Chinese: Children < 10: parent's NESS score compared to physician assessment with NESS score using a weighted Kappa score. Children ≥ 10: parent's NESS score compared to physician assessment with NESS score using a weighted Kappa score. Children ≥ 10: child's	70 (36 <10 years old, 34 ≥ 10 years old, and up to 18 years)	< 10 years old (mean 6.5 ± 2.3, range 4 months to 10 years old) ≥ 10 years old (16 parents completed forms, mean 12.5 ± 1.7 years old. 18 children completed forms mean 13.8 ± 2.0) Patients with atopic exzema recruited from outpatient clinic.		Validity - Criterion: All children: physicians assessed NESS compared to physician SCORAD scores R^2 = 35.5% Children < 10: parent's NESS compared to physician NESS scores: weighted kappa score 0.79 (95% CI 0.70-0.91)('substantial') Children ≥ 10: parent's NESS compared to physician NESS scores: weighted kappa score 0.85 (95% CI 0.69-1.00)('good') Children ≥ 10: child's NESS compared to physician NESS scores: weighted kappa score 0.74 (95% CI 0.36-1.00)('substantial') Children < 10: parent's NESS compared to physician SCORAD scores: R^2 = 42.1% Children ≥ 10: parent's NESS compared to physician SCORAD scores: R^2 = 47.5% Children ≥ 10: child's NESS compared to physician SCORAD scores: R^2 = 49.8% Agreement between the NESS from parents or patients and physicians: Bias = 0.47 (mean difference between the paired means) limit of agreement was -	No clinical outcomes are reported comparing the use of patients and parents assessment of atopic eczema severity with NESS translated in to Chinese and physicians assessed NESS or SCORAD. There is no objective measure for the results of the statistical analysis. The questionnaire was completed by all within 1 minute.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
		own NESS score compared to physician assessment with NESS score using a weighted Kappa score. (The kappa score was interpreted as; κ≤0.20 =poor agreement, ≥0.21 κ ≤0.4 =moderate agreement, ≥0.41 κ ≤0.60 =substantial and >0.80 =good) Children < 10: parent's NESS score compared to physician assessment with SCORAD score using a Bland and Altman plot. Children ≥ 10: parent's NESS score compared to physician assessment with SCORAD score using a Bland and Altman plo				2.49 to 3.43.	
Housman TS;Patel MJ;Camacho F;Feldman SR;Fleischer AB;Balkrishnan R; 2002 Dec [46]	Study Type: Other Evidence Level: II	Intervention: SA-EASI (SA=self assessment) EASI The SA-EASI was divided into acute (erythema, induration and excoriation) and chronic (dryness, lichenification, and oozing/crusting) SA-EASI Comparison: Validity – Criterion: Agreement between total SA-	47	Children < 12 years of age (unknown mean and range) Diagnosis of atopic dermatitis. Recruited from outpatient clinics Unknown inclusion/exclusion criteria		Validity – Criterion: Correlation between total SA-EASI and EASI, pearson's rho = 0.62, p<0.0001 Correlation between acute SA-EASI subscale and acute EASI subscale, pearson's rho = 0.60, p<0.0001 ('relatively high') Correlation between chronic SA-EASI subscale and chronic EASI subscale pearson's rho = 0.62, p<0.0001 Subcomponents of SA-EASI:	No clinical outcomes are reported comparing the use of self assessment of atopic eczema and the physicians assessment of atopic eczema.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
		EASI and total EASI, acute and chronic SA-EASI subscales using measure of agreement by simple linear regression according to Pearson's correlation. Correlation of sub components of SA-EASI and EASI. Correlation of sub components of SA-EASI and EASI				Correlation between visual analogue scale intensity rating from the SA-EASI (redness, thickness and scratchiness) and corresponding individual components of EASI scale (average erythema, induration and excoriation) pearson's rho range 0.17-0.30. When weighted for body surface area correlation between: SA-EASI redness and EASI erythema pearson's rho = 0.57. SA-EASI thickness and EASI induration pearson's rho = 0.53. SA-EASI scratchiness and EASI excoriation pearson's rho = 0.59. Correlation between visual analogue scale dryness rating from the SA-EASI and corresponding individual components of EASI scale (average dryness, lichenification and oozing/crusting) pearson's rho range 0.32-0.45. When weighted for body surface area the correlation between 'chronic' SA-EASI and EASI oozing gave a pearson's rho = 0.49, 'chronic' SA-EASI and EASI dryness pearson's rho = 0.63 and 'chronic' SA-EASI and EASI lichenification pearson's rho = 0.59. Correlation between visual analogue scale itch rating from the SA-EASI and the acute EASI scale score pearson's rho = 0.54 (p = 0.0001). When weighted for body surface area the pearson's rho = 0.65. Correlation between visual analogue scale itch rating from	

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
						the SA-EASI and the chronic EASI scale score pearson's rho = 0.58 (p = 0.0001). When weighted for body surface area the pearson's rho = 0.66. Correlation between body surface area SA-EASI estimates determined by survey co-ordinator and the EASI estimates determined by the physician was pearson's rho = 0.55 (p = 0.0001). Regression showed EASI body surface area scores significantly predicted the SA-EASI scores (p < 0.00010) explaining 0.29 of the variation.	
Chamlin SL;Kao J;Frieden IJ;Sheu MY;Fowler AJ;Fluhr JW;Williams ML;Elias PM; 2002 Aug [68]	Study Type: Other Evidence Level: II	Intervention: SCORAD	24	Mean age 6.4 years, range 1.5-12 years	Construct validity SCORAD correlated with measurement of changes in transepidermal water loss SCORAD correlated with Hydration determined by electrical capacitance SCORAD correlated with measurement of stratum corneum integrity, determined by sequential tape stripping. Sensitivity to change Before and after using ceramide-dominant, physiologic lipid-based emollient, using one-way analysis of variance.	Construct validity SCORAD correlated with, measurement of changes in transepidermal water loss: for involved skin r = 0.6388, p < 0.0001, uninvolved skin r = 0.4274, p < 0.0001. Hydration determined by electrical capacitance in involved skin r = -0.4373, p < 0.0001, no correlation with uninvolved skin. Stratum corneum integrity in involved skin r = -0.3453, p < 0.05. Sensitivity to change Significant change in SCORAD after treatment compared to before treatment, p < 0.5.	TEWL and hydration are not measured in clinical practice
Hon KL;Leung TF;Ma KC;Li AM;Wong Y;Li CY;Chan IH;Fok TF;	Study Type: Other Evidence Level: 3	Intervention: SCORAD and NESS correlation using pearson's chi squared SCORAD and urinary	126	children aged under 18 years (mean age 9.4 =/- 4.2)		SCORAD and NESS correlation: r=0.681, p < 0.0001 SCORAD and urinary leukotriene E4 corelation; r=0.681, p<0.0001	Urinary leukotriene E4 levels are not measured in clinical practice

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
2004 May 61		leukotriene E4 correlation using pearson's chi squared NESS and urinary leukotriene E4 corRelation using pearson's chi squared Comparison:				NESS and urinary leukotriene E4 corelation; not significant no numbers given.	
Lob-Corzilius T;Boer S;Scheewe S;Wilke K;Schon M;Schulte Im WJ;Diepgen TL;Gielere U;Staab D;Werfel T;Schmid-Ott G;Fartasch M;Wittenmeier M;Schnopp C;Kupfer J;Schlippe AV;Szczepanski R;Keins P; 2004 56	Study Type: Other Evidence Level: II	Intervention: Skin Detectives Questionnaire SCORAD	183	Study children aged 8 to 12 years with atopic eczema, SCORAD >20	Correlation between the components of the 'Skin Detectives Questionnaire' assessed by patient and components of SCORAD assessed by expert: The degree of severity for dryness in non-inflamed areas, redness in inflamed areas, knotty swellings or small visible blisters, weeping or scabbing, traces of scratching, deep creases.	Correlation between the components of the 'Skin Detectives Questionnaire' asses by patient and components of SCORAD assessed by expert: dryness in non-inflamed areas; r = 0.229, p = 0.001, n = 185 redness in inflamed areas; r = 0.213, p = 0.002 knotty swellings or small visible blisters; r = 0.084, p = 0.126 weeping or scabbing; r = 0.272, p = 0.000 traces of scratching; r = 0.214, p = 0.001 deep creases; r = 0.286, p = 0.000	There is no objective measure for the results of the statistical analysis.
Oranje AP;Stalder JF;Taieb A;Tasset C;De LM; 1997 Feb 73	Study Type: Other Evidence Level: 3	Intervention: The percentage of photos scoring below, within and above the range of the experts for the overall global symptom score or the other intensity items (erythema, oedema/papulation, oozing/crusting, excoriation, lichenification).	27 photographs	27 photographs , examined by 69 paediatricians and 22 paediatric dermatologists or physicians with dermatological experience. Included in systematic review[39]		Interobserver variability: The percentage of photos scoring below, within and above the range of the experts showed that doctors without dermatological experience underscored erythema (p<0.001). There was no difference in the overall global symptom score or the other intensity items (oedema/papulation, oozing/crusting, excoriation, lichenification). The study found the interobserver variability to be better in trained dermatologists	No details of the patients in the photos were given.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
						than non-dermatologists.	
Schafer T;Dockery D;Kramer U;Behrendt H;Ring J; 1997 Oct [72]	Study Type: Other Evidence Level: 3	Intervention: SCORAD		171 children aged 5-6 years old. Study included in the systematic review[37]	Time to complete SCORAD Interobserver variability (9 physicians) for: Total SCORAD Overall intensity Erythema Oedema Oozing lichenification Excoriation	No longer than 10 minutes to complete SCORAD Interobserver variability for: Total SCORAD: p = 0.002 Overall intensity: p = 0.000 Erythema: p = 0.174 Oedema: p = 0.058 Oozing: p = 0.617 lichenification: p =0.000 Excoriation: p = 0.033	
Holm EA;Jemec GB; 2004 Nov [79]	Study Type: Other Evidence Level: 3	Intervention: N/A Comparison: N/A	42	Children aged 1-15 years (mean 7 SD 4.2) with atopic eczema recruited from an outpatient dermatology clinic. Mean objective SCORAD score 23.2 (across 65 visits).	1) Time spent on eight different activities and their correlation* to SCORAD (mean [range] minutes per day) 2) Test-retest (n=10)	1) topical application 29 (1-150), p=0.017 washing 8.8 (0-60), p=0.05 avoiding irritants 6.2 (0-90), p=0.036 sleep loss 15.7 (0-360), p=0.013 buying/obtaining treatment 1.6 (0-8), p=0.003 visiting GP 0.2 (0-4), p=0.625 visiting specialist 0.1 (0-2), p=0.599 visiting hospital 0.8 (0.2-7.5), p=0.109 mean total 62.7 (.7-426.5), p<0.0001 2) Mean difference 0.5 (95% CI -2.161, 1.161), p=0.513	Funding: none declared. *Spearman's correlation coefficient was used to analyse the relationship between time spent on treatment and objective SCORAD, however only p values were given. Retesting was done in 10 children by telephone interview, 2 days after the first clinical interview. Time spent on traetment was calculated as the total amount of time spent daily on the different activities (minutes per day): theoretical maximum 1440 minutes. Time spent on treatment as a function of SCORAD for all visits was also shown on a graph.
Berth-Jones J; 1996 Sep [52]	Study Type: Other Evidence Level: 3	Intervention: Review of SASSAS		Study included in the systematic review [52]		It takes 2 to 10 minutes to complete the SASSAD score. The score has been used for monitoring the progress of individuals in the dermatology clinic.	

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
						It has been used in a community based study to assess atopic eczema in 1 year-old babies	
Verwimp JJ;Bindels JG;Barents M;Heymans HS; 1995 Sep 43	Study Type: Other Evidence Level: 3	Intervention: Use of two different whey-protein hydrolysate based formulas Measurement using BCSS	175	Infants from 50 baby health clinics suspected of having cow's milk protein intolerance. Study included in the systematic review.[39]		Children showed a significant improvement from baseline using BCSS	
Koning H;Neijens HJ;Baert MR;Oranje AP;Savelkoul HF; 1997 Jun 532	Study Type: Other Evidence Level: 3	Intervention: Total serum IgE and Interleukin-13 and SCORAD were measured	27 Children with atopic eczema aged 7 to 50 months (mean age 27 months) 42Children without atopic eczema, allergic or non-allergic asthma aged 5 to 59 months (mean age 28 months) Study included in the systematic review [39]			SCORADs correlation with Interleukin-13, rs = 0.47, p = 0.0074, n = 32	There is no objective measure for the results of the statistical analysis. Interleukin 13 level is not measured in clinical practice
Berth-Jones J;Finlay AY;Zaki I;Tan B;Goodyear H;Lewis-Jones S;Cork MJ;Bleehen SS;Salek MS;Allen BR;Smith S;Graham-Brown RA; 1996 Jun 64	Study Type: Other Evidence Level: 3	Intervention: Cyclosporine investigated for efficacy, safety and tolerability of cyclosporine SASSAD used to evaluate outcome	27	Children with severe atopic eczema aged 1 to 16 years old Study included in the systematic review [39]		Children showed a significant improvement from baseline in SASSAD	
Frezzolini A;Paradisi M;Ruffelli M;Cadoni S;De PO; 1997 Jan	Study Type: Other Evidence Level: 3	Intervention: Soluble CD30 an activation marker of T-cell clones able to produce Th2-type cytokines and Costa's SSS were measured	25	Children with atopic eczema aged 2 to 8 years old Study included in the systematic review [39]		Costa's SSS correlation with soluble CD30, r = 0.508, p = 0.01	There is no objective measure for the results of the statistical analysis. Soluble CD30 not measured in clinical practice

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
[533]		Comparison: Correlation between soluble CD30 and Costa's SSS					
Charman C;Venn AJ;Williams HC; 1999 [77]	Study Type: Other Evidence Level: 3	Intervention: Measurement of body surface area, using 'rule of nines' by 6 dermatologically trained observers. Level of agreement for the classification of scores into quintile categories was 55% Comparison:	6	Adults and children with atopic eczema (aged 4 to 51 years unknown mean age) Study included in the systematic review [39;39]		Median score ranged from 4.8% to 37.2% Level of agreement for the classification of scores into quintile categories was 55%, with a chance corrected agreement (kappa statistic) of 0.09 - representing very poor interobserver agreement.	Adults and children used in study mean age unknown Measurement of extent of disease rather than total severity
Hon KL; 2006 Jun [71]	Study Type: Evidence Level: 3	Intervention: SCORAD index as a tool for measuring severity of AE. Comparison: SCORAD index versus sleep loss and pruritus	182	Children under 18 with atopic eczema. Mean age 9.6 years (SD 4.2).	SCORAD, comparison of subjective (pruritus, sleep loss) and objective items (extent, intensity)	Extent vs pruritus: r =0.42 Extent vs sleep loss: r=0.38 Intensity vs pruritus: r=0.38 Intensity vs sleep loss: r=0.34 All with p<0.005	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Sarkar R; Raj L; Kaur H; Basu S; Kanwar AJ; Jain RK; 2004 [84]	Study Type: Case-control Evidence level: 2-	n=22 children with atopic eczema n=20 healthy age & sex matched controls plus mothers of the above	Children with atopic eczema aged 3-9 years Mild to severe cases with 64% moderate Severity of the disease was graded according to Rajka & Langeland criteria	Intervention: None Comparison: psychological status of mothers and their eczematous children with mothers and their healthy children	Follow-up period: None Outcome Measures: Hindi adaptation of Personality Trait Inventory (PTI) for mothers (maternal personality and mental distress) Childhood Psychopathology Measurement Schedule for the children (CPMS) (low intelligence with behavioural disorders, conduct disorders, anxiety and depression)	Mothers: An increased number of mothers of affected children 13 (59%) were found to be submissive compared to the mothers of the controls 2 (10%) p<0.01 Children: There was a higher frequency of low intelligence with behavioural disorders (5.9 SD2.9) with children of atopic eczema compared to healthy controls and also of conduct disorders (2.1 SD 1.4) p<0.01 for both Anxiety (1.6 SD 1.7 vs. 0.6 SD 1.0) and depression (2.7 SD 2.7 vs. 0.7 1.0) was also more frequent in children with atopic eczema. p<0.05 for both	Study is EL= 2- as it is a non-randomised controlled study Small study not carried out in the UK. However, it used standard and validated questionnaires for assessing psychological disturbances. Important to note PTI comprised of 90 questions, CPMS comprised of 51statements The funding of the study is unknown
Absolon CM; Cottrell D; Eldridge SM; Glover MT; 1997 [81]	Study Type: Case-control Evidence level: 2-	n= 30 children with atopic eczema n= 30 children with relatively minor skin lesions such as viral warts	School aged children mean age 8.7 years Severity of eczema was varied	Intervention: None Comparison: psychological problems of children with atopic eczema and children with minor skin lesions	Follow-up period: None Outcome Measures: Children: Rutter parent scale (psychological problems) Mothers: General Health Questionnaire (GHQ) (mental distress) Family Support Scale	The Rutter scale showed twice the rate of psychological disturbance was found in children with eczema compared with the control group (Overall p=0.063; 95%CI -6 to +48%) The difference was statistically significant for children with moderately severe and severe eczema (Chi squared = 5.6; p=0.018) but not for children with very mild eczema. GHQ showed levels of mental distress of mothers were no different between groups (p=0.58) There was no difference in the degree of social support experienced by the families. Both	Study is EL= 2- as it is a non-randomised controlled study Small study but based in UK. Rutter scale has been used in 80 countries, consists of 31 statements General Health Questionnaire consists of 28 questions Family Support Scale rates amount of help from 18 sources on a scale of 0-5. The funding of the study is unknown

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						groups had an average of 8 sources of informal support each and they rated these supports as similarly helpful.	
Walker C; Papadopoulos L; Hussien M; Lipton M; 2004 85	Study Type: Case-control Evidence level: 2-	n= 85 children with eczema n= 45 children with asthma n= 36 healthy children	Children aged between 7 & 12 years old No details on severity of eczema	Intervention: None Comparison: illness beliefs and psychosocial morbidity between children with eczema, asthma and no health problems	Follow-up period: None Outcome Measures: Children's Illness Perception questionnaire (CIPQ) adapted from the adult version 26 items The Piers-Harris Children's Self-concept Scale	Results suggested that the children with eczema felt greater consequences as a result of their disease than those with asthma In terms of psychosocial morbidity, the children's understanding of the consequences of their disease was more important than the presence or visibility of the condition.	Study is EL= 2- as it is a non-randomised controlled study. This study was funded by Remedi (disability charity).
Andreoli E; Mozzetta A; Palermi G; Paradisi M; Foglio Bonda PG; 2002 86	Study Type: Other Evidence level: 3	n= 490 subjects with a variety of skin diseases of which n=88 had atopic eczema	Subjects were aged 1-17 years and had various skin diseases at different levels of severity mean age of male eczema patients 8.35 years mean age of female eczema patients 9.82 years	Intervention: None Comparison: None	Follow-up period: None Outcome Measures: Psychopathological diagnosis according to the American Psychiatric Association's diagnostic and statistical manual of mental disorders ed 4 (DSM/IV)	Atopic eczema is strongly correlated: -During ages 1-9 years with attention deficit/hyperactivity disorder (10%) and with mental retardation (4%). All cases were male. -During early adolescence (10-17 years) with general anxiety disorder (13%) and with dysthymic disorder (6%) (both predominantly in female cases)	Study is EL= 3 as it is an uncontrolled study. The funding of the study is unknown
Moore K; David TJ; Murray CS; Child F; Arkwright PD; 2006 87	Study Type: other Evidence level: 3	n=92 parents of 55 children, 26 of which had eczema (others had asthma)	Children with moderate to severe eczema or asthma	Intervention: None Comparison: sleep and quality of life of parents of children with atopic eczema and asthma	Follow-up period: None Outcome Measures: Parents sleep disturbance Hospital and Anxiety Depression Scale (HADS)	Sleep: Mothers lost median of 39 and fathers 45 minutes sleep per night with children with atopic eczema compared to 0 minutes in parents with children with asthma ($p<0.001$) this effect was independent of whether a one or two parent family. HADS Depression score of mothers	Study is EL= 3 as it is an uncontrolled study, using a non-specific scale to determine the anxiety and depression of parents with children with atopic eczema The funding of the study is unknown

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						looking after a child with eczema was twice that of mothers of children with asthma Univariate analysis eczema vs. asthma odds ratio 2.0 (1.1-3.6) p value =0.02 using multivariate analysis this association was found to be due to lack of sleep rather than the child's eczema per se 1.1 (0.5-2.4) p value =0.8	
Ricci G; Bendabdi B; Aiazzi A; Masi M; 2004 [88]	Study Type: Other Evidence Level: 3	Intervention: Educational and medical programme of 6-two hour sessions Comparison: None	n=17 families of children	Children with atopic eczema (no details although SCORAD used) aged 5 months to 48 months and their parents	Fava-Kellner Symptom questionnaire at beginning and end of study Satisfaction questionnaire at the end of study	Symptom questionnaire values improved over study but were still greater than normal values. No statistics presented	Study is EL= 3 as it is an uncontrolled study. The funding of the study is unknown

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Study summary
Carr A;Patel R;Jones M;Suleman A; 2007 [501]	Study Type: OtherPre-post non-randomised, uncontrolled pilot study. Evidence Level: 3	Intervention: Appointment with community pharmacist: interview about current treatment practices advice on and demonstrations and explanations on best practice on use of emollients. Comparison: Before and after intervention	50	Children aged 1 to 7 years with AE and their parents	Itch Irritability Sleep disturbance Skin appearance	Reduction in itch:1.48 (p=0.001) Reduction in irritablity: 1.23 (p=0.006) Reductioni n sleep disturbance: 0.34 (p=0.44) Reduction in skin appearance:0.75 (p=0.09)	Pharmacists can deliver education on effective use of emollients and this is valued by parents.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Lewis-Jones MS; Finlay AY; 1995 [82]	Study Type: Evidence Level: 3	Intervention: None Comparison: None	Part One n= 169 children and their parents in a dermatology clinic Part Two n=40 children with their parents in a dermatology clinic Part three n=233 children with their parents in a dermatology clinic n=47 healthy control children n=55 controls attending a general paediatric clinic	Children aged 3-16 years with skin diseases and have presented at a paediatric dermatology department	Part one: Children with the help of their parents were asked to write down all the ways their skin disease affected their lives. From the above information a 10 question questionnaire was devised Part two: This draft questionnaire was piloted and minor alterations were made to improve clarity Part three: The questionnaire (CDLQI) was given to 233 dermatology patients and 102 control patients Part four: 46 children completed the CDLQI on two occasions with a 4 day interval to check reliability of questionnaire	Part one: 111 different aspects of how skin disease affected children's and their family's lives were identified and from these 10 questions were composed using a structure similar to the Adult Dermatology Life Quality Index Part two: Part three: The CDAQI scores for eczema (mean =7.7, 5.6, n=470), psoriasis (5.4,5.0,n=25) and acne (5.7,4.4, n=40) were all significantly greater than moles and naevi (2.3,2.9,n=29) Part four: Test-retesting showed that the SD of the differences between pairs of data (2.5) was significantly less than the SD of the measurements themselves (before=4.79, after= 5.08)	Study is EL= 3 as it is a non-intervention mainly uncontrolled study. The funding of this study was not declared.
Ben-Gashir MA; Seed PT;HayRJ; 2004	Study Type: Other Evidence Level: 3	Intervention: None Comparison: None	n=78 at first visit of which n=71 attended the second visit and were included in the analysis	Children with atopic eczema (mean age 8.6 years) in primary care	SCORAD CDLQI	The children's QOL was affected in 65 (92%) and 55 (77%) children attending the first and second visits. The CDLQI was significantly correlated with the SCORAD at the first and second	The study is EL=3 as it is an uncontrolled validation study. The funding of this study was not declared.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
[75]						visits (r=0.52, r=0.59, respectively p<0.001 for both) Each unit change in the SCORAD was associated with a 0.12 (95% CI 0.04-0.19, p=0.004) unit change in the children's quality of life.	
Noor Aziah MS; Rosnah T; Mardziah A; Norzilla MZ; 2002 [104]	Study Type: Other Evidence Level: 3	Intervention: None Comparison: None	n=72 children of which n=70 children completed the DFI and n=33 completed the CDLQI	Children aged between 6 months and 16 years (mean 74 months) with atopic eczema Mean SCORAD 38.9 SD15.5 at first visit	Malay version of CDLQI and DFI SCORAD Scored at 0 and 2 weeks	SCORAD First Visit: Mean SCORAD 38.9 (SD 15.5) Second visit: Mean SCORAD 34.6 (SD 16.4) (p=0.003) CDLQI: Visit 1: Mean score 10.0 (SD 6.6) Visit 2: Mean Score 7.6 (SD 6.2) Mean score for mild atopic eczema 6.5(SD 7.8 n=2) Mean score for moderate atopic eczema, 8.8 (SD 5.9 n=21) Mean score for severe eczema 13.2 (SD 7.1 n=10) The highest scoring items were itchiness and soreness (1.8, SD 0.7), emotional disturbance (1.2, SD 1.0), Leisure activities (1.0, SD 0.9), school disturbance (1.1, SD 0.9) and sleep loss (1.2 SD 1.8) DFI First Visit: Mean DFI 9.4 (SD 5.3) Second visit: Mean DFI 7.8 (SD 4.8) Mean score for mild eczema 5.2 SD 4.4,n=5	This study is EL=3 as it is uncontrolled. The funding of this study was undeclared Further validation of the DFI examining internal consistency and repeatability

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						Mean score for moderate 8.5 SD 5.1, n=38 Mean score for severe eczema 11.5 SD 5.2, n=27 p=0.02 between moderate and severe cases The highest scores were for sleep loss, parents emotional disturbance, exhaustion, questions regarding diet and treatment Internal consistency (Cronbach alpha score)of the DFI was 0.85 (10 items tested n=70) Validity of questions (Kappa analysis) showed an average of moderate agreement	
Beattie PE; Lewis-Jones MS; 2006 90	Study Type: Other Evidence Level: 3	Intervention: None Comparison: None	n= 379 children and their parents	Children (aged 5-16 years) with a skin disease of more than 6 month's duration and their parents	CDLQI completed by children CLQI completed by the parents	Using linear regression analysis, the CLQI and CDLQI scores showed a strong linear association (r_s=0.72, p<0.001) and on a Bland-Altman plot, reasonably good agreement (expressing scores out of 100, the 95% limits of agreement were from -25.5/100 to 26.7/100). In the child's opinion psoriasis and atopic eczema caused the greatest impairment (CDLQI 30.6%, 30.5% respectively). Using the generic CLQI (parental perspective) the highest score was for atopic eczema (33%).	Study is EL= 3 as it is an uncontrolled non-intervention study The funding of this study was not declared.
Holme SA; Man I; Sharpe JL; Dykes PJ; Lewis-Jones MS; Finlay AY; 2003 106	Study Type: Other Evidence Level: 3	Intervention: None Comparison: None	Part one (pilot): n=101 children completed both cartoon and written CDLQI in a random order in clinic n= 66 children completed the cartoon CDLQI both in clinic	Part one: Children with a median age of 11 years. The most common diagnoses were naevi (22%), acne (21%), atopic dermatitis (17%), viral warts (13%)	Written CDLQI Cartoon CDLQI with the aim of the study to validate the cartoon version against the already	Part one: There were no statistical differences between written and cartoon versions of CDLQI (p=0.405) in clinic. 42 (64%) cartoon CDLQI questionnaires were received from the second test-retest. A significant difference was found between the two scores (Kruskall-Wallis	This study is EL=3 as it is an uncontrolled validation study. The funding of this study was not declared.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
			and at home within one day Part two: n=107 children completed both cartoon and written CDLQI in a random order in clinic Part three: n=546 children reviewed in clinic were send either the written or cartoon version of the CDLQI to complete and return by post.	and psoriasis (9%) Part two: Children with a median age of 11 years. The most common diagnoses were eczema (20%), acne (12%), psoriasis (12%), viral warts (11%) and naevus (10%) Part three: The median age of children was 12 years. No details on diagnoses	validated written CDLQI	test p=0.029) Part two: There was no significant difference between the scores of the cartoon and written ones (p=0.427) and analysis suggested no period (p=0.203), carry-over (p=0.233) or treatment (p=0.355) effect. The cartoon version was completed faster (median 90 seconds) than the written version (median 120 seconds) (p<0.0001) Both children and parents preferred the cartoon version to the written version (63% children, 68% parents) and found it easier to use (69% children, 67% parents). Part three: 249 questionnaires were returned. 46% response rate (126 cartoon,123 text)	
Lewis-Jones MS; Finlay AY; Dykes PJ; 2001 [102]	Study Type: Other Evidence Level: 3	Intervention: None Comparison: None	n= 102 parents of children with atopic eczema (n=34 recruited by post, 68 from outpatients)	Predominantly Caucasian infants under 4 years with atopic eczema	Infants' Dermatitis QOL index (IDQOL) DFI Parents were asked to complete the IDQOL and DFI on two separate occasions to test repeat validity Infant's behavioural Check List (BCL)	Return rate for initial questionnaires 87.3% (61boys,28 girls) Retest 70.6% Mean score for IDQOL was 7.89 and for DFI 8.87 Spearman rank correlation between IDQOL and DFI was high, r=0.87 Correlations of IDQOL and DFI with clinical severity was lower, r=0.58, r=0.5 respectively Test-retest data for IDQOL and DFI confirmed repeatability (Bland and Altman)	Study is EL= 3 as it is an uncontrolled non-intervention study. The funding of this study was undeclared.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						The highest scoring questions for DFI were parental sleep disturbance, tiredness and exhaustion and emotional distress	
Beattie PE; Lewis Jones MS; 2006? [103]	Study Type: Other Evidence Level: 3	Intervention: The impact of an initial consultation with a dermatology clinic Comparison: Comparing the parent's assessment of their child's eczema with the IDQOL and DFI. Comparison of IDQOL and DFI measures at two consecutive visits.	n=203 parents of infants with atopic eczema filled in the DFI and IDQOL once. n=50 of the above completed both questionnaires at the first and second visit.	n=203 Parents of children with atopic eczema aged 0-4 years, median age 16 months (SD 13.3 months) of the n=50 group median age 12 months (SD 10.4) Severity assessed by the parent: n=5 clear n=75 fairly good n=68 average n=48 severe n=7 worst ever	IDQOL DFI	The group of n=203 infants: The mean IDQOL and DFI were 8.47 (SD 5.8, 6.5 respectively). Good correlation of the above r_s=0.79 95% CI 0.73-0.84) Parent's assessment of eczema correlated well with IDQOL (r_s=0.6 CI 0.5-0.69) but less well with the DFI (r_s=0.4, CI 0.27-0.51) Highest scoring IDQOL items were: Itching and scratching, problems at bath time, time to fall asleep. Highest scoring DFI items were: Tiredness and exhaustion sleep loss and emotional distress. In both measures these items also correlated most strongly with eczema severity The group of n=50 who completed questionnaires at visit 1 and 2: Between visits 1 & 2 median eczema severity score fell from 2 (SD 0.83) to 1(SD 0.8) (CI 0.5 to 1) Median IDQOl fell from 8 (SD 5.92) to 5 (SD 5.92) (CI 2 to 5.5) Median DFI score fell from 9.62 (SD 6.45) to 5.49 (SD 6.56) (CI 2 to 5.5) The most improved IDQOL items were time taken to get off to sleep, difficulties at mealtimes The most improved DFI items were tiredness, exhaustion and emotional	This study is EL=3 as it is a survey with no control group. The funding of this study was undeclared.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						distress in parents.	
Lawson V; Lewis-Jones MS; Finlay AY; Reid P; Owens RG; 1998 [92]	Study Type: Case-control Evidence level: 2-	n= 73 families with a child with atopic eczema n= 50 families with no atopic eczema n= 56 questionnaires were completed and returned	Families with children with atopic eczema rated by the investigator using standard criteria	Intervention: None Comparison: Families with children with atopic eczema compared with families with children unaffected by eczema	Follow-up period: None Outcome Measures: 10 question one-page Dermatitis Family Impact (DFI) questionnaire	In the eczema group the mean DFI score was 9.6+/-7.0 (range 0-27, n=56) In the unaffected families the mean score was 0.4+/- 0.9 (range 0-3, n=26, p<0.0001) The highest scoring questions were treatment, sleep, tiredness and distress	Study is EL= 2-as it is a controlled study. This study was partially funded by the National Eczema Society UK This study developed the DFI by qualitative interviews, testing a detailed questionnaire and then producing the 10 question DFI. Only the results of the latter stage have been detailed in this table
Ben-Gashir MA; Seed PT; Hay RJ; 2002 [74]	Study Type: Other Evidence Level: 3	Intervention: None Comparison: None	n= 116 children on first visit n= 106 children on second visit and this number was used in analysis	Children with atopic eczema aged 5-10 years with 80% of these diagnosed as mild by the SCORAD index	Modified form of the SCORAD index, (SCORAD-D) DFI tested at 0 and 6 months	First visit (n=116, mean age 8 years): Family QOL affected in 48 (45% of cases) Mean DFI 2.4 SD4.4 Mean SCORAD-D 8.2 SD10.2 Second visit (n=106, mean age 8.5 years: Family Qol affected in 38 (36% of cases) Mean DFI 1.9 SD4.2 Mean SCORAD-D 7.7SD8.7 Changes in the DFI were significantly related to changes in the SCORAD-D (regression coefficient ; 0.17 (95%CI 0.06-0.29, p=0.002) After adjusting for potential confounders each unit increase in the SCORAD-D lead to a 0.25 (95% CI 0.11-0.4, p=0.001) and 0.23 (95% CI 0.05-0.42, p=0.014) increase in the DFI for the first and second visits respectively	Study is EL= 3 as it is an uncontrolled study. The funding of this study was not declared. Further validation of the DFI confirming its association with severity of disease No analysis of test-retest validity although data appears to support validity
McKenna SP; Whalley D; de Prost Y; Staab D; Huels J; Paul CF; van Assche D;	Study Type: Other Evidence Level: 3	Intervention: None Comparison: None	After 65 qualitative interviews with parents in the UK, Netherlands and Italy and field-test interviews with approximately 20	Parents with children with atopic eczema	International development of PIQoL-AD Validation within different countries (languages)	Application of the Rasch model to the survey data identified the final 28 item version All language versions had	Study is EL= 3 as it is an uncontrolled non-intervention study. The study was funded by Novartis Pharma AG (Basel, Switzerland).

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
2006 [107]			children in each country to assess face and content validity, the instrument was finalised with the following numbers of children with atopic eczema and their parents in each of the following countries UK n=328 Netherlands n=45, France n=209 Germany n=78 US n=48 Spain n=153		Evaluation of psychometric properties	a)good item fit b)test-test reliability: all co-efficients above the minimum acceptable level of 0.85 c)internal consistency: Cronbach's coefficients for the PIQoL-AD varied between 0.88 and o.93 at time 1 and between 0.88 and 0.93 at time 2 d)promising validity	Evidence for validity of PIQoL-AD across 7 European countries
DM Meads; McKenna SP; Kahler K; 2005 [108]	Study Type: Systematic review - meta-analysis Evidence level: 1+	n=621 data from four trials Trial A: Two US trials consisting of 199 and 206 participants aged up to 18 years. These trials were double-blind for 6 weeks followed by an open-label period lasting 20 weeks measuring QoL and disease severity at 0, 6 weeks and 6 months. Other trials were multinational Trial B: 733 children up to 18 years Trial C: 255 children aged up to 2 years These trials lasted 12 months and compared active with conventional	Children with atopic eczema and their parents	Intervention: Comparison: None	Follow-up period: None Outcome Measures: Secondary analysis of The Parents Index of Quality of Life in Atopic Dermatitis (PiQoL-AD) data to interpret the meaningfulness (significance) of the QoL results with anchor-based and distribution-based methods	Anchor-based analysis The overall correlations for each time point (baseline, 6, 26 and 52 weeks) in each trial indicated generally low levels of association between PiQoL-AD scores and clinical indicators EASI (0.35), IGA, (0.26) PRU(0.35)and SA (0.32) Large CI of PIQoL-AD meant limit to usefulness of clinical relevant conclusions. When data from all time points were combined, it showed a clear progression in mean PIQoL-AD scores with increasing severity of measures (EASI,IGA,PRU,SA) although correlation was still low PIQol-AD scores varied by scores on all four anchor measures (p<0.001) Distribution-based analysis This was used to determine effect size, which was similar across all trials: 1.2 points =small effect 3 points= moderate effect 5 points= large effect	Systematic review is EL= 1+ as it consists of RCTs. The funding of this study was undeclared. it was not clear in the text exactly such studies the data came from

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
		treatment Assessments of QoL and disease severity were at 0,6 weeks, and 12 months. The PIQoL -AD was only completed by parents of children aged 8 years or younger who lived in countries in which a validated version of the measure was available.				These results indicate that a change of 2 to 3 PIQoL-AD points over time could be considered meaningful.	
Chamlin SL; Frieden IJ; Williams ML; Chren MM; 2004 [111]	Study Type: Evidence Level: 3	Intervention: None Directed focus sessions were performed with the parents to determine quality of life effects Comparison: None	n=26 parents of children with atopic eczema	Children aged birth to 6 months with atopic eczema after initial diagnosis. Recruitment was not based on severity of disease Children with comorbid medical conditions that required daily or frequent medical care were excluded	to document the effects of atopic eczema on young children and their families	Parents and experts mentioned a total of 181 specific quality of life effects. From these documented effects a conceptual frame work was developed containing the domains of physical health, emotional health, physical functioning and social functioning. Each domain includes effects on both the child and the parents.	This study is EL=3 as it is non-interventional explorative study. It was funded by a grant from the Society for Pedriatric Dermatology (USA)
Chamlin SL; Cella D; Frieden IJ; Williams ML; Mancini AJ; Lai JS; Chren MM; 2005[112]	Study Type: Other Evidence Level: 3	Intervention: None Comparison: None	n= 270 parents of children with atopic eczema	Children with atopic eczema under the age of 6 years and their parents	Testing of the validity of CADIS and to refine it	Exploratory factor analysis of the entire sample results in the removal of nine items e.g. item 18 was removed for low factor loading, four items were reviewed and removed that were ambiguous, biased or wordy. Rasch analysis resulted in elimination of three further items e.g. for the symptoms domain, three items had a high Mean Square fit Statistics (MnSq) and were eliminated Five further items were removed because many parents chose the same response	Study is EL= 3 as it is an uncontrolled study. The funding of this study was partially supported the Society for Pediatric Dermatology, The American Skin Association and the National Institute on Arthritis and Musculoskeletal and Skin Diseases USA.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						Based on the results of psychometric analyses and item performance results the framework was modified to a five scale framework Internal consistency was acceptable for all scales: alpha results and item total correlation range shown for each Family and social function 0.91, 0.48-0.81 Emotion scale: 0.92, 0.42-0.75 Sleep scale: 0.76, 0.54-0.66 Symptoms scale: 0.93, 0.70-0.84 Activity limitations and behaviour scale: 0.84,0.39-0.69 270 parents responded with 453 mentions of the way atopic eczema bothered their child and 410 mentions of the ways it bothered them. The three most common issues were itching/scratching, pain/discomfort and sleep issues. All mentions noted by 7% or more parents were included in CADIS items	
Su JC; Kemp AS; Varigos GA; Nolan TM; 1997 [7]	Study Type: Cohort Evidence level: 2-	n=48 children with atopic eczema n= 46 children with insulin dependent diabetes mellitus	Children with atopic eczema aged 4 months to 15 years, mean age 4.5 (SD 4.2 years) Eczema severity scored by the Rajka and Langeland: n=10 severe,n=20 moderate, n=18 mild	Intervention: None Comparison: The score on a family impact questionnaire (Stein and Riessman), the economic cost of treatment and the loss of earnings between the two groups eczema and diabetes	Follow-up period: None Outcome Measures: The impact on family questionnaire of Stein and Riessman Financial costs were assessed by a questionnaire consisting of 4 sections: the cost of medication over past 12 months; the	Impact on family score: Severe eczema 2.61 (CI 2.3 to 2.9) (p=0.0002 compared to diabetes group) Moderate eczema 2.31 (2.0 to 2.6) (p=0.0032 compared to diabetes group) Mild eczema 1.97 (1.7 to 2.2) (p=0.41 compared to diabetes group) All patients with eczema 2.25 (CI 2.1 to 2.4)	This study is EL-2 as it is a cross sectional survey of children with eczema with a control (reference) group of children with diabetes. The funding of this study was undeclared.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
					number of visits to health professionals over last 12 months; the number of hospital admission days over past 12 months and indirect costs contributing to income loss e.g. days off work Numbers of hours of sleep loss over past 3 months from observations and records	(p=0.0012 compared to diabetes group) Diabetes 1.85 (1.7 to 2.0) Costs to the community were great in terms of visits to health professionals and hospitalisation. An estimate of the annual personal financial cost of managing mild moderate and severe eczema was AUS $330,818 and 1255 respectively. and this was considered to be greater than looking after children with asthma. The mean (SD) hours of sleep lost by parents averaged 3(2.8) hours for severe group, 3(1.7) hours for moderate and 2 (1.5) hours for the mild group The mean (SD) hours of sleep lost by children averaged 2(2.1) hours for severe group, 2(1.4) hours for moderate and 1 (1.1) hours for the mild group	
Zuberbier T; Orlow SJ; Paller AS; Taieb A; Allen R; Hernanz-Hermosal; Ocampo-Cadiani J;Cox M; Langeraar J; Simon JC; 2006 [96]	Study Type: Other Evidence Level: 3	Intervention: None Comparison: None	n=2002 with atopic eczema of which n=779 are children with aged 2-13 years.	Children with moderate to severe atopic eczema as defined by their physician/GP.	In depth telephone or face to face interviews using a non standard questionnaire consisting of 37 single and multipart questions for parents/carers looking after children aged 2-13 years. The questions were divided into sections including sections on the effect of an atopic eczema flare on daily life, emotional aspects of atopic eczema and one section on	Effect of atopic eczema on daily life (average figure): Total duration of flare (14 days) No. of days in flare per year (121.8) No. of nights sleep affected during a flare (5) No. of times woken up at night during a flare (1.8) Percentage of patients (%) avoiding at least 1 everyday activity (86%) School life affected (30%) Home life affected (33%) Social life affected (27%) Percentage of time at work/school performance affected during flare (7%) No of days absent from school-work	The study is EL=3 as it is uncontrolled. The funding of this study is undeclared. This is a large, up to date record of children's and their families experiences of atopic eczema.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
					quality of life using the PIQoL-AD	because of a flare (2 days) Percentage of patients during an atopic flare Fairly/very concerned about being seen in public (29%) With effect on self confidence (24%) Unhappy or depressed (52%) Have been bullied or teased because of their atopic eczema (25%) Percentage of patients where atopic eczema has an effect on other household members (37%) PiQoL results reflected the above results with 71% taking care over clothes, 64% worrying about possible side effects of treatment, 63% worrying about the child's looks, 52% felt they had no control over the atopic eczema, 46% worrying about the future of their child.	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Follow-up and outcome measures	Effect size	Reviewer comments
Dennis H; Rostill H; Reed J; Gill S. 2006 [89]	Study Type: Case series Evidence Level: 3	n=353 of which n=74 completed survey (21% response rate)	Children aged 5 to 11 years (mean age 7.1 years SD =1.9) with atopic eczema (equal numbers of mild, moderate and severe diagnosed by consultant dermatologist) but no other serious medical conditions	Child Behaviour Checklist (CBCL) General Health Questionnaire version 28 (GHQ-v28) DFI Family Environment Scale (FES) The parent of each child was sent a letter inviting them to participate and all the relevant forms regarding the above with a stamped addressed envelope for return. Severity of eczema was assessed for medical record once consent was obtained.	Data of interest and its analysis was presented as opposed to all data from outcome measures. Severity of eczema had no statistically significant effect on child adjustment (internalising and externalising) scores or parental psychological adjustment (p>0.05 for all) Family adjustment (DFI) was significantly affected by the severity of the child's atopic eczema (p<0.01) Bonferroni analyses indicated this difference was between mild and severe categories. CBCL data showed that 27.4% of the children showed internalising behaviour and 9.6% showed externalising behaviour this compares to 18% and 17% respectively in the general population. Further analysis showed a positive association between internalising and parental psychological wellbeing (p=0.02), family impact (p=0.02) and negative association with supportive family environment (p<0.01) There was also a significant negative assocation with externalising and a supportive family environment (p=0.01)	The data presented in this paper is hard to interpret as it is not presented as a whole rather as select complex analysis [EL=3] The funding of this study is undeclared.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Follow-up and outcome measures	Effect size	Reviewer comments
Hon KLE; Kam WYC;Lam MCA; Leung TF; Ng PC; 2006 105	Study Type: Cross-sectional Evidence level: 2-	n=80 42 boys, 38 girls	Children (mean age 11.7 SD 3.7 years) with atopic eczema as diagnosed by Hanifin and Rajka criteria.	Follow-up period: none Outcome Measures: SCORAD (and objective SCORAD) and NESS for severity of atopic eczema. CDLQI for quality of life IgE and eosinophil counts	Median scores (interquartile range) SCORAD 56.1 (45.8-71.4) NESS 14 (12-15) CDQLI 10 (7-13) Total CDLQI weakly correlated with total SCORAD (Spearman coefficient =0.23, p<0.05) Total CDLQI and total NESS poorly correlated (Spearman coefficient =0.29, p<0.05) No correlation for objective SCORAD and CDLQI (Spearman coefficient =0.17, p>0.05) Median serum IgE and eosinophil counts and percentages did not correlate with CDLQI Spearman coefficient 0.191, 0.136 and 0.098 respectively.	Median scores were used through out and thus the two extremes of quality of life and severity were not represented. The funding of this study was undeclared.

Epidemiology

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Bohme M;Svensson A;Kull I;Nordvall SL;Wahlgren CF; 2001 Jun 149	Study Type: Case-control Evidence level: 2-	320 (221 cases, 99 controls)	Part of a community-based birth cohort of 2256 children (the BAMSE study). Cases (those with an itchy rash for 2 weeks or more) first seen at the clinic before 25 months of age were included. At about 2 years (median 25 months, range 20-29 months) children with atopic eczema were systematically re-examined. Controls were also examined at about 2 years (median 27 months, range 23-32 months). They had no history of eczema at 1 or 2 years (questionnaire and telephone interview respectively).	Intervention: Cases - children with atopic eczema Comparison: Control group - no atopic eczema	Follow-up period: Outcome Measures: 1) Sensitisation* 2) Sensitisation and severity of AE (SCORAD)	1) 27% had at least one positive skin prick reaction. Positive reactions: 21% to hen's egg white, 15% peanut, 8% cow's milk, 2% cod, 2% wheat, 1% soya. The IgE test result was positive in 15%. 2) No data, but it was reported that there was no significant difference in objective SCORAD scores in sensitised and non-sensitised cases with ongoing eczema.	Funding:Swedish Asthma and Allergy Association, the Swedish Foundation for Health Care Sciences and Allergy Research. All skin examinations were carired out by the same dermatologist. The Hanifin and Rajka criteria were used to diagnose atopic eczema. *Specific IgE to inhalants and foods were measured in 212 cases (96%). Results were recorded as positive or negative (not defined). Skin prick testing was done in 97% of cases. A positive reaction was defined as a reaction at least half the diameter of the reaction to the positive control, and not less than 3mm in diameter.
Bieber T; 2002 114	Study Type: Systematic review - meta-analysis Evidence level: 3	30 studies (26 in children)	Adults and children	Intervention: Search of Medline (1966 to August 2000) and Embase (1977 to August 2000) Study type not restricted. English language only.	Follow-up period: Outcome Measures: Prevalence	30 studies published between 1990 and 2000 (26 in children). In UK (5 studies): 14% (n=322) aged 1-4 years (history and examination by trained observer in 1992). 10.7% (n=413) in 1 year olds	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
				Prevalence of atopic eczema Comparison: NA		(dermatologist examination, 1993) 11.7% (n=693) in 3-11 year olds, dermatologists examination, 1994) 8.5% (n=695) in 3-11 year olds, dermatologists examination, 1995) 14.2% (n=260) in 4 year olds (dermatologists examination, 1996) 12-month period prevalence 16.5% (by history and dermatologists examination in 1 to 5 year olds, n = 695)	
Williams H; 2000 [115]	Study Type: Systematic review - meta-analysis Evidence level: 3	8 studies	Adults and children	Intervention: Epidemiological data Comparison: N/A	Follow-up period: Outcome Measures: Age of onset Location Severity Long term prognosis Concurrent asthma, hay fever and allergic rhinitis	8 studies identified based in hospital patients or specialist clinics. The age of onset of atopic eczema was before 1 year of age in between 42% (n = 100) and 88% (n = 121) of the children. The review also found two studies investigating the age of onset of atopic eczema in the community. One a historical cohort study based in the UK found 66% developed atopic eczema by the age of 7 years (n = 6877, up to the age of 16). The second study, a retrospective questionnaire, found 63% developed atopic eczema by the age of 7 years (n = 694, aged 14 years). Severity of atopic eczema reported in 5 studies. “65 to 90% of cases in the community being mild	The author was contacted for methodological details of this review. He confirmed that this was conducted as a systematic review, although the search strategy, inclusion/exclusion criteria etc were not specified in the chapter and so the review cannot easily be replicated/updated using information from the book chapter alone, and therefore the review has been assigned an evidence level of 3 (as a narrative review)

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						severity and 1 to 2% classified as severe" 25 studies investigated the long-term prognosis of atopic eczema; 22 included children aged under 12 years at study inception (studies were reported between 1930 and 1997). Data for studies that included children at inception are reported here. The countries in which the studies were conducted were not clear. Most of the studies included individuals who had been treated as hospital inpatients or outpatients. Data were gathered by questionnaire and/or physical examination; losses to follow-up were common, ranging from about 3% to 73% (median 31%). The studies suggest that atopic eczema is a chronic condition, with a 10-year clearance rate of 50-70%, although a wide range of clearance rates over varying follow-up periods have been reported (11-92%). Several studies found that individuals who were apparently clear of atopic eczema subsequently experienced a relapse at a later point, which may reflect differences in use of terms such as clearance and remission. 6 studies reported concurrent or subsequent asthma, hay fever or allergic rhinitis: Asthma in 10 to 53% Hay fever in 33 to 78%	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						Allergic rhinitis in 12 to 28%.	
Vicencio JCA;Gonzalez-Andaya AM; 2005 150	Study Type: Cross-sectional Evidence level: 3	50	Children aged 2 months to 16 years (mean 3.5 years), diagnosed with atopic eczema using Hanifin and Rajka criteria. 66% of the children had mild atopic eczema, 28% moderate and 6% severe (measured using the SASSAD scale). 42% had a personal history of atopy (52% asthma, 19% allergic rhinitis, 24% asthma and allergic rhinitis, 5% urticaria).	Intervention: Sensitisation to different allergens at different ages Comparison: N/A	Follow-up period: Outcome Measures: 1) Sensitisation 2) Relationship between atopic eczema and sensitisation	1) Positive skin prick test: 64% (51.5% of those with mild atopic eczema, 88.2% with moderate-severe). 2) A significant association between sensitisation to food and/or inhalants and the severity of atopic eczema was reported (p=0.033). Odds of developing moderate/severe eczema was 4.4 times greater in children who developed sensitisation to any one of the allergens than in those who did not (95%CI 1.06-18.2).	Funding: none declared. Skin Prick Tests; in children 2 years or younger the following allergens were tested: cow's milk, egg white and yolk, shellfish, soya, tuna, peanut, HDM,cat pelt, dog epithelium, Bermuda grass and Kapok. Children older than 2 years were tested for the following allergens Cow's milk, egg yolk and white, fish, soy, tuna, peanut, wheat, cocoa bean, HDM, cat pelt, dog epithelium, Bermuda grass, Acacia, Kapok, mixed moulds, and cock roach. A positive skin test was given by a wheal size that measured at least 3mm in diameter, or a wheal that was larger than the negative control (saline).

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
Ben-Gashir MA;Seed PT;Hay RJ; 2004 Mar [133]	Study Type: Other Evidence Level: 3	Intervention: Survey of children with atopic eczema from general practices, involving an interview and clinical examination. Looked at atopic eczema: Severity using SCORAD Age at first presentation Concurrent conditions Comparison:	137	Children aged 5 to 10 years old who were diagnosed with eczema	1) Severity 2) Age at first presentation 3) Concurrent conditions	1) Mild (SCORAD ≤15) in 80%, Moderate (SCORAD 16-40) in 18% Severe (SCORAD >40) in 2% 2) < 1 year 68% (93/137) 1-2 years 16% (21/137) 2-6 years 13% (18/137) ≥7 years 3% (4/137) Odds ratio for severity: If onset was during first year of life: non adjusted 2.1 95% CI 1.2-3.3, p = 0.006 Adjusted 2.1 95% CI 1.2-3.2, p = 0.008 3) Asthma: 43% (59/137) Hay fever: 45% (62/137) Asthma and/or Hay fever: 64% (87/137) Odds ratio for severity: If child also had Asthma: non adjusted 1.95 95% CI 1.34-3.34, p = 0.016 Adjusted 2.0 95% CI 1.1-3.6, p = 0.021 If child also had Hay fever: non adjusted 2.49 95% CI 1.44-4.3, p = 0.001 Adjusted 2.42 95% CI 1.39-4.2, p = 0.002	As only children aged 5-10 years old were included in the study the children who developed atopic eczema at a later age would not have been included, leading to an increased number of children developing eczema at an early age. Likewise the study would have missed the children who developed asthma or hay fever at a later age, leading to an underestimate in the children who had concurrent asthma and hay fever.
Broberg A;Svensson A;Borres MP;Berg R; 2000 Nov [534]	Study Type: Other Evidence Level: 3	Intervention: Questionnaire asked: 1. Has your child ever had eczema? 2. Does your child have active eczema? Clinical examination performed by dermatologist	1961	Children scheduled for a health visit at 5.5 years of age, 1219 in Goteborg and 742 in Kristianstad Sweden	Prevalence	Parental reporting: Active eczema 16%, 167/1219 in Goteborg and 16%, 119/742 in Kristianstad Eczema any time 37%, 447/1219 in Goteborg and 33%, 243/742 in Kristianstad (overall 690/1961, 35.2%) Never had eczema 63%, 772/1219 in Goteborg and 67%, 499/742 in Kristianstad	Funding: Swedish Asthma Allergy Association

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
		Severity Comparison:				Of children reported to have active eczema by parents, on examination by a dermatologist the point prevalence was 8.5% (95% CI 7.0, 10.1) in Goteberg, and 11.5% (9.2, 13.8) in Kristianstad. Severity of visible eczema (In 155/157 children with visible eczema at examination): Mean SCORAD score 20.5 (95% CI 18.7 to 22.3), median 19.6	
Emerson RM;Williams HC;Allen BR; 1998 123	Study Type: Other Evidence Level: 3	Intervention: Questionnaire survey Comparison: N/A	1760	Children aged 1-5 years from general practices in Nottingham	1) 12 month period prevalence 2) Referral rate 3)	1) 16.5% 2) 6% (17/290; 11 to hospital dermatologist, 4 to private dermatologist, 2 to paediatrician, and 6 to accident and emergency) Referral rate was higher in severe disease (43%) than moderate (15%) or mild (3%).	Funding: Novartis AE diagnosed by a dermatologist. Reasons for referral were not given.
Burr ML;Butland BK;King S;Vaughan-Williams E; 1989 Oct 535	Study Type: Other Evidence Level: 3	Intervention: Surveys undertaken in 1973 and 1988. Comparison: N/A	965	Children aged 12 years in South Wales.	Eczema prevalence ('ever')	4.8% in 1973 15.9% in 1988 (difference 11.1, 95% CI 8.4, 13.8)	The main aim of the study was to record asthma prevalence but some data for eczema were also reported.
Williams H;Robertson C;Stewart A;it-Khaled N;Anabwani G;Anderson R;Asher I;Beasley R;Bjorksten B;Burr M;Clayton T;Crane	Study Type: Other Evidence Level: 3	Intervention: Comparison:					

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
J;Ellwood P;Keil U;Lai C;Mallol J;Martinez F;Mitchell E;Montefort S;Pearce N;Shah J;Sibbald B;Strachan D;von ME;Weiland SK; 1999 Jan 124							
Aoki T;Fukuzumi T;Adachi J;Endo K;Kojima M; 1992 135	Study Type: Other Evidence Level: 3	Intervention: Evaluation of which parts of the body are affected by atopic eczema Comparison: N/A	1012 (812 [80.2%] of whom had an atopic history)	Infants and children aged less than 10 years with possible AE attending dermatology clinic, January 1989-December 1990.	Area affected by atopic eczema	in infants aged 3-5 months, 81% cheeks, 62% forehead, 61% scalp, 42% chin. On trunk, 67% chest, 64% back, 59% abdomen IN children aged 5-9 years, 50% neck, 38% nape, 16% scalp, 25% perioral, 33% forehead, 40% cheeks.	52 skin regions were examined for the presence of lesions Data for change in incidence by age were shown in graphs. Involvement of the cheeks, forehead, scalp, chin, periauricular regions, and ankle regions decreased with age. Involvement of inguinal regions, buttocks, para-axillar regions, hips, cubital and popliteal fossae, knees and elbows increased with age. Only areas with highest % shown in this table.
Harris JM; 2007 127	Study Type: Other Evidence Level: 3	Intervention: Epidemiological data Comparison: N/A	592	Children aged 8 years from a birth cohort in Kent.	1) Lifetime prevalence 2) Annual period prevalence (range)	1) 25.3% at age 8 (56.7% identified before age 2 years). 2) 8.3-10.6%	Funding:Colt Foundation UK Working party criteria were used to diagnose AE. Recruitment to the cohort started in November 1993.
Ninan TK;Russell G; 1992 Apr 4 116	Study Type: OtherSurvey Evidence Level: 3	Intervention: Questionnaire survey of parents, regarding asthma, eczema, hay fever	2510 in 1964 and 3403 in 1989	Children aged 8-13 years attending primary schools in Aberdeen. Questionnaires were administered to	1) Point prevalence of atopic eczema	1) 5.3% in 1964, and 12% in 1989	Funding: Astra Pharmaceuticals, A&H, National Asthma Canpaign

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
		Comparison: N/A		parents and guardians of the children.			
Kulig M;Bergmann R;Klettke U;Wahn V;Tacke U;Wahn U; 1999 Jun [140]	Study Type: Other Evidence Level: 3	Intervention: Prevalence and incidence rates of allergic sensitisation Comparison: N/A	216	A sub-cohort of children from the German MAS study (Bergmann 1994[139]) - those with complete specific IgE data at the ages of 1, 2, 3, 5, and 6 years.	1) Point prevalence of allergic sensitisation to at least one of the tested allergens 2) Annual incidence rates of sensitisation	1) 11% (95% CI 7, 15) at 1 year, and 30% (24, 36) at 6 years To inhalant allergens: 1.5% (95% CI 0, 3) at 1 year, and 26% (20, 32) at 6 years To food allergens: 10% (95% CI 6, 14) at 1 and 6 years 2) To one of four food allergens: 10% (6, 14) at 1 year, and 3% (1, 5) at 6 years. To at least 1 inhalant allergen: 1.5% (0, 3) at 1 year, and 8% (4, 12) at 6 years. From age 3 years specific IgE to inhalant allergens were significantly higher than specific IgE levels to food allergens in children of the same age, p<0.006.	Funding: As for Bergmann.[139] The incidence rate was defined as the proportion of children with sensitisation (specific IgE level of 0.7 or more) in the group of children at risk (children originally free of sensitisation in whom it could have developed during the period). Prevalence = the proportion of sensitised children (specific IgE of 0.7 ku/l or more) in the total group at the respective time point).
Wang IJ;Lin YT;Yang YH;Chen CL;Tsai YH;Chiang BL;Hwang KC; 2004 Oct [146]	Study Type: OtherCross-sectional study Evidence Level: 3	Intervention: Sensitisation to inhalant and food allergens Comparison: N/A	262	Children aged 0-16 years with atopic eczema. 10% were aged under 2 years, 52% aged 2-5 years, and 39% aged more than 5 years. Severity was assessed in 31%, using SCORAD; 19% had mild eczema, 55 moderate, and 26% severe.	1) Sensitisation 2) Association between allergens and age (sex-adjusted OR) 3) Risk of concomitant asthma and allergic rhinitis	1) 57% had elevated total IgE levels. 2) Food allergy: 2.58 (1.07, 6.21) in those aged <2 years; 1.09 (0.58, 2.05) in children aged 2-5 years, and 0.57 (0.29, 1.13) in children older than 5 years. Inhalant allergens: Der pteronyssinus 0.02 (0.002, 0.142) in those aged <2 years; 0.72 (0.44, 1.91) in children aged 2-5 years, and 4.28 (2.41, 7.59) in children older than 5 years. Der farinae 0.02 (0.003, 0.159) in those aged <2 years; 0.72 (0.44, 1.18) in children aged 2-5 years, and 4.02 (2.30, 7.05) in children older than 5 years. Cockroach; no data for those	Funding: none declared. Asthma diagnosed if there were more than 4 attacks of wheezing in the past 12 months or 1-3 wheezing episodes in addition to night awakening for wheezing, nocturnal cough, and wheezing after exercise. Sensitisation was defined as elevated IgE levels of at least one of the allergens tested (5 inhalant allergens, 6 food allergens). A specific IgE of more than 0.7ku/l and a total IgE level of more than 200ku/l was considered positive.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
						under age 2 years, 0.45 (0.18, 1.10) in children aged 2-5 years, and 3.53 (1.45, 8.61) in children older than 5 years. 3) Asthma: no data for those aged <2 years; 0.58 (0.34, 0.99) in children aged 2-5 years, and 3.26 (1.88, 5.65) in children older than 5 years. Allergi rhinitis: 0.05 (0.01, 0.24) in those aged <2 years; 0.55 (0.33, 0.90) in children aged 2-5 years, and 4.63 (2.65, 8.09) in children older than 5 years.	
Wolkerstorfer A;Wahn U;Kjellman NI;Diepgen TL;De LM;Oranje AP; 2002 Jan 536	Study Type: OtherCase series (the placebo arm of the ETAC RCT). Evidence Level: 3	Intervention: Sensitisation to cow's milk and egg, and its relationship to the severity of atopic eczema. Comparison: N/A	382	Children in the placebo arm of the ETAC RCT. Infants aged 1-2 years with a positive history of atopy and active symptoms of atopic eczema. Most had mild to moderate atopic eczema (mean SCORAD score of 20).	1) Proportion with sensitisation to cow's milk and egg 2) Severity (mean SCORAD scores) according to sensitisation 3) Correlation between the severity of atopic eczema and degree of sensitisation at different follow-up visits (Spearman rank correlation) 4) Change in sensitisation (change in RAST class of at least one class) over time	1) At inclusion (study start): 36% cow's milk, 50% to egg. 88% of those sensitised to cow's milk were also sensitised to egg. 33% were sensitised to egg only. 'During the follow-up sensitisation remained stable for cow's milk and decreased slightly for egg' (no further details). 2) 17.9 (SD 10) in children with normal specific IgE. 18 (SD 10) in children with specific IgE to cow's milk only, 20.5 (12) with specific IgE to egg only, and 23.1 (SD 12) with specific IgE to to both cow's milk and egg. High levels of specific IgE (17/5 ku/l or more) were reported to be more common in children with moderate to severe atopic eczema (data shown in graphs only). 3) Baseline 0.16 (cow's milk), 0.22 (egg), p<0.005 for both At 3 months: 0.09 (cow's milk) and 0.15 (egg; p=NS and p<0.05 respectively) At 12 months: 0.12 (cow's milk) and 0.16 (egg), p<0.05 for both	Funding: none declared. Specific IgE levels were determined using the Pharmacia CAP system. Sensitisation = an IgE level of 0.35ku/l or more.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
					in relation to percentage improvement in objective SCORAD score	At 18 months, 0.15 (cow's milk) and 0.21 (egg), p<0.05 and p<0.005 respectively. 4) Sensitisation increased; mean improvement in objective SCORAD 35.8 (SD 58) cow's milk, and 38.1 (54) egg. Sensitisation unchanged: mean improvement in objective SCORAD 34.1 (SD 75) cow's milk, and 33.2 (81) egg. Sensitisation increased: mean improvement in objective SCORAD 9.5 (SD 75) cow's milk, and -6.9 (71) egg.	
Wuthrich B;Schmid-Grendelmeier P; 2002 [145]	Study Type: Other Evidence Level: 3	Intervention: Natural history of AE Comparison: N/A	22	Children with AE seen at the age of 2-4 years, and re-evaluated at age 10-12 years. No other demographic data	% with 1) AE 2) asthma 3) allergic rhinitis 4) positive skin prick test 5) elevated IgE levels (according to age values - no further details) 6) Sensitisation to foods (IgE test) - egg white, cow's milk, cod, wheat, peanut, soy 7) Sensitisation to inhalant	All results are for age 2-4 years then 10-12 years 1) 100% vs 68% 2) 9% vs 45% 3) 0% vs 41% 4) 54% vs 77% 5) 41% vs 81% 6) 41% vs 27% 7) 50% vs 80%	Funding: none declared Swiss cohort.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
					allergens (HDM, grass, tree pollen)		
Bohme M;Lannero E;Wickman M;Nordvall SL;Wahlgren CF; 2002 138	Study Type: Other Evidence Level: 3	Intervention: Cohort of children recruited at their first visit to child health centre during first months of life. At the time of recruitment the parents filled in a questionnaire concerning environmental and heredity factors. At 1 or 2 years there was another questionnaire on atopic disease. Atopic eczema Concurrent conditions	3791		1) Period prevalence 2) % with concurrent conditions	1) 25.1% atopic eczema during their first 2 years (952/3791) 2) Asthma: 2.9% (109/950). Ratio of asthma in children with atopic eczema over those without atopic eczema: 1.45, 95% CI 1.16-1.80. Allergic rhinoconjunctivitis 3.1% (115/936). Ratio of allergic rhinoconjunctivitis in children with atopic eczema over those without atopic eczema: ratio 2.25, 95% CI 1.77-2.85. Adverse reactions to food:10.7% (405/946). Ratio of adverse reactions to food in children with atopic eczema over those without: 3.20, 95% CI 2.83-3.62.	Funding: none declared Ratio adjusted for heredity
Bohme M;Wickman M;Lennart NS;Svartengren M;Wahlgren CF; 2003 Sep 537	Study Type: Other Evidence Level: 3	Intervention: Questionnaire: Lifelong prevalence	4089 children born between Feb 1994 and 1996 aged 0-4			Lifelong prevalence: 33% had symptoms of atopic eczema	
Eigenmann PA;Sicherer SH;Borkowski TA;Cohen BA;Sampson HA; 1998 143	Study Type: Other Evidence Level: 3	Intervention: Specific IgE antibody concentrations to 6 foods was evaluated. Comparison: N/A	63	Children and adults with atopic eczema aged 0.4-19.4 years, median age 2.8 years who were referred to a dermatologist. Patients had persistent eczematous rash in two or more predilection sites despite the use of topical corticosteroids and who presented to	1) IgE levels 2) Results of DBPCFC (n=19 of 41 with a positive IgE result)	1) 65% (41/63) of children with eczema had positive IgE values (more than 0.7ku/l) to at least 1 of 6 foods tested 2) 18 positive challenges in 11 patients. There were no reactions to placebo.	Group who were tested were a select group may not be representative of all children with atopic eczema. Positive IgE test: more than 0.7 ku/l (i.e. these were considered to be allergic to foods (this was then tested by DBPCFC). The foods tested were milk, egg, peanuts, fish, soya, wheat.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
				the dermatology clinic. Median SCORAD score 41 (range 6.5-94.5), mean 43.			
George S;Berth-Jones J;Graham-Brown RA; 1997 Apr 129	Study Type: Other Evidence Level: 3	Intervention: Parents of children interviewed at 1 year of age about atopic eczema. Point and lifetime Prevalence of atopic eczema Severity of atopic eczema (mean SASSAD score) Consultations by general practitioner and referral to a dermatologist	499 children from a cohort of 1800		1) Point prevalence of atopic eczema 2) Severity of atopic eczema (mean SASSAD score)	1) Asian children: 12/134 (9%) Non-Asian children: 32/279 (11.5%), p = 0.55 95% CI -3.8% to 8.9% Lifetime prevalence atopic eczema: Asian children: 21/134 (15.7%) Non-Asian children: 43/279 (15.4%), p = 0.94 95% CI -7% to 7% 2) Asian children: 6.3 SD 3.7 Non-Asian children: 7.3 SD 3.5	Funding: Leicester Dermatology Research Foundation
Halkjaer LB;Loland L;Buchvald FF;Agner T;Skov L;Strand M;Bisgaard H; 2006 May 538	Study Type: Other Evidence Level: 3	Intervention: Prevalence of atopic eczema	411 infants. Children followed from birth to 3 years, visits every 6 months		Cumulative incidence	44% (155/356) at 3 years (Hanifin and Rajka criteria). Severity of eczema (SCORAD) was assessed every 6 months. The proportions with mild, moderate or severe eczema changed as follows from age 6 months to 3 years: mild 43% - 81% moderate 56% - 17% severe 2% - 2% Prevalence shown in graphs only.This peaked at 2 years in boys and 2.5 years in girls.	Funding: none declared. Study undertaken in Copenhagen
Heinrich J;Hoelscher B;Frye C;Meyer I;Wjst M;Wichmann H; 2002	Study Type: Other Evidence Level: 3	Intervention: Three cross-sectional regional surveys in 1992-1993, 1995-1996 and 1998-1999. Some children participated in two or three surveys investigating the	7632 children aged 5-14 years recruited form Schools in Germany		1) Adjusted prevalence	1) Survey 1992-1993 Children aged 12 at survey (born 1981) 9.6% Children aged 9 at survey (born 1984) 8.6% Children aged 6 at survey (born 1987) 8.6%	No statistical analysis given and some children participated in two or three surveys.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
[118]		prevalence of atopic eczema.				Survey 1995-1996 Children aged 12 at survey (born 1984) 9.1% Children aged 9 at survey (born 1987) 9.9% Children aged 6 at survey (born 1990) 11.0% Survey 1998-1999 Children aged 12 at survey (born 1987) 10.2% Children aged 9 at survey (born 1990) 11.8% Children aged 6 at survey (born 1993) 13.0%	
Hill DJ;Hosking CS; 2004 [144]	Study Type: Other Evidence Level: 3	Intervention: Epidemiological data Comparison: N/A	487 (those with complete data from questionnaires, of n=620)	Infants aged up to 120 months from the Melbourne Atopy Cohort study (commenced in 1990). They were recruited on the basis of one or more parents or siblings having either atopic eczema, asthma, hay fever, or severe reactions to foods.	1) Cumulative prevalence of atopic eczema 2) Prevalence of IgE mediated food allergy 3) Prevalence of IgE mediated food allergy linked to severity of AE	1) 28.9% (n=141) 2) 35% of those with AE, and 12% of those without AE, p<10(-6) RR of AE because of IgE-mediated food allergy for children with AE = 3.1 (2.1, 4.4) 3) Increased with severity	Funding: Victorian Department of Human Services, Nestle and the Royal Children's Hospital Melbourne. Skin prick tests to common allergens and foods undertaken at 6 and 12 months of age. Mothers were encouraged to delay the introduction of solids until after the age of 6 months when low allergen solids were introduced (not egg, peanut or fish). Modified UK Working party diagnosis criteria used to diagnose eczema. Negative skin prick test = no greater than control. IgE mediated food allergy = if the mean wheal diameter to any of 3 food extracts was at least twice the histamine reference standard.
Illi S;von ME;Lau S;Nickel R;Gruber	Study Type: Other	Intervention: Survey of children followed up aged 1,3,6,12,18 and 24 months and one a	1314 (of 7609 infants born in 1990). 1123 were analysed as	Birth cohort study	1) Prevalence of atopic eczema	1) 13.4% in first year of life. Lifetime prevalence by the age of 2 years: 241/1123 (21.5%)	Funding: none declared. German Multicenter Atopy Study (MAS). 499

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
C;Niggemann B;Wahn U;Multicenter Allergy Study Group.; 2004 May 134	Evidence Level: 3	year up until 7 years old. Parents questions about atopic eczema symptoms and severity. Comparison: N/A	they completed at least one follow up.		2) Scratching as a prognostic factor for AE 3) Any sensitisation (IgE 0.35ku/l or more) at age 2 years as a prognostic factor for AE 4) Having a cat in early childhood as a risk factor for AE	Of children with early manifestations of atopic eczema: n =192 Of children with an onset in the first year of life, 43.2% were in complete remission after age 2 years 55.4% only had symptoms in the first year of life 18.7% had symptoms of atopic eczema every year up to the age 7 years 38% had an intermittent pattern of eczema up to 7 years 2) 72.2% of children with persistent AE reported frequent scratching with early AE compared with 35.6% of those with an intermittent pattern, and 14.5% of the children with complete remission after 2 years, adjusted cumulative odds ratio 5.86 95% CI 3.04-11.29 3) Cumulative OR 2.52 (1.62 to 3.90) 4) Cumulative OR 2.33 (0.85 to 6.38)	of the children had risk factors for atopy (increased cord blood IgE [0.9ku/l or more], at least 2 atopic family members, or both), and 815 newborns with none. AE diagnosed through questions on questionnaire.
Kuehr J;Frischer T;Karmaus W;Meinert R;Barth R;Urbanek R; 1992 Dec 539	Study Type: Other Evidence Level: 3	Intervention: Questionnaire completed by parents asking about eczema	1376	Children aged 6-8 years	Point prevalence	17.3%	Funding: German Federal Ministry for Research and Technology
Kurukulaaratchy R;Fenn M;Matthews S;Hasan AS; 2003 Jun	Study Type: Other Evidence Level: 3	Intervention: Visit to research centre , telephone questionnaire or postal questionnaire: Life long prevalence Current incidence	1456	All children born on the Isle of Wight between in January 1989 and February 1990 Aged 10 years old	1) Prevalence of atopic eczema 2) Onset of atopic eczema	1) 1 year old: 9.6% 132/1374 2 years old: 10.3% 127/1231 4 years old: 11.9% 145/1214 Life long prevalence at 10 years: 41.0% Incidence in last year at 10 years:	The definition for atopic eczema unclear. For incidence of atopic eczema in the last year 'itchy rash occurring in the last 12 months and had previously been given the diagnosis of eczema'. The paper also considers risk actors for AE

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
126		Onset				13.7% 186/1358. 56.3% still had the condition at age 10 years. 2) 71.0% of children with current eczema developed it before the age of 4 years	such as food allergy, and smoking. Data not reproduced here.
Lehtonen EP;Holmberg-Marttila D;Kaila M; 2003 Oct 540	Study Type: Other Evidence Level: 3	Intervention: Retrospective chart review of children born in 1994. Data gathered for atopic eczema	320	Children born 1974 in Finland.	1) Cumulative prevalence	1) 16% at age 5 years (95% CI 12, 20). 49% were diagnosed between the ages of 6 to 24 months. 30% were recorded as having 'food-related' problems	Funding: none declared. Data gathered by retrospective chart review. No specific diganostic criteria were used for AE (classified as AE if those words or words to that effect were used in the notes).
McNally NJ;Williams HC;Phillips DR;Strachan DP; 2000 Apr 128	Study Type: Other Evidence Level: 3	Intervention: Data from the National Child Development Study, 1958 birth cohort. Parental reporting of eczema, from examination by a health visitor. Comparison:	8278	Children born in 1958n study who had information on presence or absence of visible eczema at all ages (7, 11 and 16 years).	Prevalence	Eczema prevalence (%) and adjusted odds ratio (OR (95%CI) p value) Reported by 7 years: North west: 5.3%, 1.00 (base) Northern: 5.4%, 1.03 (0.67-1.59) p > 0.05 East and West Ridings: 7.8%, 1.50 (1.01-2.23) p > 0.05 North Midlands: 8.7%, 1.61 (1.08-2.41) p < 0.05 Eastern: 10.8%, 2.03 (1.41-2.93) p < 0.001 London and south East: 8.2%, 1.48 (1.05-2.09) p < 0.05 Southern: 10.1%, 1.89 (1.28-2.81) p < 0.01 South Western: 8.0%, 1.51 (1.00-2.28) p > 0.05 Midlands: 7.6, 1.45 (0.98-2.15) p > 0.05 Wales: 6.4%, 1.18 (0.73-1.91) p > 0.05 Scotland: 5.6%, 1.10 (0.74-1.62) p > 0.05	Cohort of children born in 1958. Pre 1975 county boundaries were used. Funding: Department of Geography, University of Nottingham, and the British Skin Foundation.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
						Eczema identified on examination: North west: 2.3%, 1.00 (base) Northern: 2.1%, 0.95 (0.49-1.83) p > 0.05 East and West Ridings: 2.3%, 0.98 (0.51-1.89) p > 0.05 North Midlands: 4.7%, 2.02 (1.15-3.56) p < 0.05 Eastern: 4.0%, 1.66 (0.94-2.91) p > 0.05 London and south East: 2.4%, 0.98 (0.57-1.70) p > 0.05 Southern: 4.7%, 2.00 (1.13-3.55) p < 0.05 South Western: 1.7%, 0.73 (0.34-1.55) p > 0.05 Midlands: 2.2, 0.97 (0.51-1.85) p > 0.05 Wales: 2.1%, 0.89 (0.41-1.94) p > 0.05 Scotland: 2.7%, 1.25 (0.71-2.20) p > 0.05	
Nnoruka EN; 2004 Oct [136]	Study Type: Other Evidence Level: 3	Intervention: Dermatological data from patients, children's parents and relatives Age of onset Location of atopic eczema Concurrent illness Comparison: N/A	1019 patients with atopic eczema from 12013 patients with skin diseases seen at skin clinic from 1998 -2000.	Age range 1 month to 59 years with average age of 13.8 years. All patients were Black	Pattern of atopic eczema	Age of onset 1-6 weeks 12.7%, 129/1019 7-12 weeks 8.1%, 83/1019 13-18 weeks 5.7%, 58/1019 19-24 weeks 4.8%, 49/1019 25-30 weeks 3.0%, 31/1019 31-36 weeks 3.6%, 37/1019 37-42 weeks 2.7%, 28/1019 >42 weeks 1.3%, 13/1019 Concurrent diseases: (Adults and children) Atopic eczema only 47.7%, 486/1019 Asthma 11.5%, 117/1019 Allergic rhinitis 4.1%, 42/1019 Conjunctivitis 1.3%, 13/1019 Concomitant respiratory allergies 35.6%, 363/1019	Adults and children included in the study, so data on concurrent illness not presented in test as unable to separate children and adult data

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
						In a control group Asthma 2.3%, 17/726 Allergic rhinitis 3.9%, 29/726 Conjunctivitis 0.7%, 5/726 Concomitant respiratory allergies 2.9%, 21/726 Location of atopic eczema 0-3 years (n = 298) Wrist extensors 27.2%, 78/298 Wrist flexors 16.7%, 48/298 Elbow extensors 38.5%, 111/298 Elbow flexors 40.1%, 115/298 Knee extensors 37.4%, 108/298 Knee flexors 17.9%, 51/298 3-18 years (n = 373) Wrist extensors 8.3%, 31/373 Wrist flexors 11.3%, 42/373 Elbow extensors 17.1%, 64/373 Elbow flexors 56.8%, 211/373 Knee extensors 15.6%, 58/373 Knee flexors 45.7%, 170/37	
Olesen AB;Bang K;Juul S;Thestrup-Pedersen K; 2005 [119]	Study Type: Other Evidence Level: 3	Intervention: Two different questionnaires sent to the different groups of children: Life long prevalence Severity Comparison: N/A	1060 children from a stratified sample of all children born between 1984 and 1986 in a maternity hospital in Denmark, surveyed in 1993. 10,000 children from a random sample of children born in Denmark from 1984 to 1994 from the Danish Medical Birth Register, surveyed in 1998.	Children aged 3 to 15 years	1) Lifelong prevalence of atopic eczema 2) Severity of atopic eczema in children born between 1984-1994 (measured on a scale of 1-7)	1) 18.9% age 7 years in the group of children born between 1984-1986 (1993 study) 19.6% age 7 years in the group of children born between 1984-1994 (1998 study) 2) Mild 47.6% 660/1385 Moderate 33.1% 458/1385 Severe 12.8%, 177/1385 (data missing on 90/1385)	Funding: Univeristy of Aarhus. Data collected by questionnaire. Definition of atopic eczema in 1993 survey unclear; UK Working Party criteria were used in 1998.
Selnes A;Bolle	Study Type:	Intervention:	10,093 in 1985 study and	Schoolchildren aged	1) Cumulative	1) 19.7% in 1995	Funding: none declared.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
R;Holt J;Lund E; 2002 Feb 120	Other Evidence Level: 3	Prevalence of atopic eczema in Norway (with further analysis for those of Sami or Norse ethnicity) Comparison: N/A	8676 in 1995 study	7-13 years in Northern Norway.	incidence of AE	13.2% in 1985	AE if there was an itchy eruption lasting for more than 4 weeks combined with lesions on the face, elbow/knee flexures, or a high degree of itching and lesions elsewhere.
Vasar M;Julge K;Bjoksto B; 2000 May 541	Study Type: Other Evidence Level: 3	Intervention: Physical examination and questionnaire	298	Healthy new born babies at term, followed up at 6, 12 and 24 months.	Point prevalence	4% (7/173) at 6 months 10.5% (23/220) at 12 months 15% (35/223) at 2 years	Criteria for AE diagnosis - Hanifin and Rajka
Wadonda-Kabondo N;Sterne JA;Golding J;Kennedy CT;Archer CB;Dunnill MG;ALSPAC Study Team.; 2003 Nov 131	Study Type: Other Evidence Level: 3	Intervention: Postal questionnaire asking parents: At the age of 6 and 18 months 1. Has the child had skin rash in joints and creases of her/his body (e.g. behind the knees, under the arms) since…? 2. Does she/he have this sort of rash now? 3. Has she/he had an itchy, dry oozing or crusted rash on the face, forearms or shins? 4. Does she/he have this sort of rash now? At the age of 30 and 42 months 5. Has the child had an itchy, dry skin rash in joints and creases of her/his body (e.g. behind the knees, elbows under the arms) since he/she was 18/30 months old? 6. Does he/she have	8530 children aged 0 to 42 months born in 1990's.		1) Period prevalence 2) Incidence	1) 0-6 months: 21.0%, 1791/8530 6-18 months: 25.6%, 2183/8530 18-13 months: 23.2%, 1975/8530 30-42 months: 19.9%, 1701/8530 2) 0-6 months: 21.0%, 1791/8530 6-18 months: 11.2%, 757/6739 18-13 months: 3.8% , 229/5982 4949/8530 (58%) had a rash at least once 622/8530 (7.3%) reported a rash on all four occasions	Funding: several sources including the MRC.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
		this sort of rash now? Study used definition of atopic eczema to be rash (from question 1, 3, or 5) Period prevalence Incidence Comparison: N/A					
Williams HC;Strachan DP; 1998 [132]	Study Type: Other Evidence Level: 3	Intervention: Parents asked by health visitors, using structured questionnaires whether their child had an eczematous rash. The presence of visible eczema was recorded by experienced school medical officers at ages 7, 11, and 16 years. Comparison: N/A	1053	UK 1958 Birth cohort study (those with data from birth and at ages 7, 11, 16, 23)	Prognosis	Of the 1053 with reported or examined eczema by age 23 years, 35% had onset in the first year of life, and 54% by aged 7 years. Of 860 with reported or examined eczema by the age of 16 years, 43% had onset by age 1 year, and 66% by age 7 years. Of those with reported or examined eczema by age 7 years, 35% still had it at 11 years, and 26% at 16 years, and 25% at 23 years. The apparent (short-term) clearance rates of 65% and 74% fell to 53% and 65% when adjusted for subsequent recurrences.	Funding: none declared.
Yura A;Shimizu T; 2001 Dec [121]	Study Type: Other Evidence Level: 3	Intervention: Lifetime prevalence Prevalence in last year	In total about 4 million	Primary school children aged 7 to 12 years. 7 population surveys carried out at 2 year intervals between 1985 and 1997 (460000-740000 per survey).	1) Lifetime prevalence 2) Prevalence in last year	1) 1985: 15.0% 1987: 19.1% 1989: 20.9% 1991: 22.0% 1993: 24.1% 1995: 22.9% 1997: 22.9% 2) 1993: 6.8% 1995: 5.6% 1997: 5.7%	
Paller AS;McAlister RO;Doyle	Study Type: Other	Intervention: Survey of children or their parents	429	Children with atopic eczema aged 15 years old or younger	1) Prevalence of asthma in children with	1) 0-2 year olds: 17.4% 21/121 3-7 year olds: 39.4% 69/175	Survey was also carried out on 2500 physicians from IMS Health (article did not state what IMS stood for) who were known to

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
JJ;Jackson A; 2002 95	Evidence Level: 3	Prevalence Age of onset Comparison: N/A		members of the National Eczema Association for Science and Education.	atopic eczema 2) Age of onset	8-15 year olds: 42.4% 53/125 2) 93% diagnosed in first 2 years of life	prescribes topical medications for treatment of atopic eczema. But only 303 (12% responded) so data not included here. Other outcomes reported in paper but not reported here as not reported by age group.
Kay J;Gawkrodger DJ;Mortimer MJ;Jaron AG; 1994 Jan 122	Study Type: Other Evidence Level: 3	Intervention: Interview by structured questionnaire Comparison: N/A	1077	Children aged 3-11 years in Birmingham.	1) One-year period prevalence (documented AE though not necessarily within the past 12 months) 2) Lifetime prevalence 3) Age of onset 4) Prevalence of asthma (at any time point)	1) 11.5% 2) 20.2% 3) Median age 6 months (0-5 months in 48%, then 7-13% maximum in every 6 month period to age 5 years, and 1-3% in every 6 month period to 10 years). 4) 38%	Funding: none declared. Atopic eczema was defined as an itchy often relapsing and lichenified dermatitis that tends to affect the face and hands in infants and also the popliteal and antecubital fossae in children aged 18 months or older.
Macharia WM 1993 137	Study Type: Other Evidence Level: 3	Intervention: Dermatological data from children aged 0-12 years Age of onset Location of atopic eczema Comparison: N/A	54 children with atopic eczema seen at a paediatric skin clinic in Kenya in 1985	Age range 0.25 to 10.25 years with average age of 3.25 years. All children were Black	Pattern of atopic eczema	Age of onset 1-3 months 58.5%; 31/53 4-7 months 5.6%; 3/53 8-11 months 17.0%; 9/53 12-23 months 1.9%; 1/53 >23 months 17.0%; 9/53 Location of atopic eczema at onset 0-11 months (n = 43) Face only 51%, 22/43 Flexure only 5%, 2/43 Extensor site only 12%, 5/43 Multiple sites 26%, 11/43 Unknown 7%, 3/43 12-23 months (n = 1) Face only 0%, 0/1	

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
						Flexure only 0%, 0/1 Extensor site only 100%, 1/1 Multiple sites 0%, 0/1 Unknown 0%, 0/1 >23 months (n=9) Face only 0%, 0/9 Flexure only 56%, 5/9 Extensor site only 11%, 1/9 Multiple sites 33%, 3/9 Unknown 0%, 0/9 Location of atopic eczema at examination 0-11 months (n = 16) Face, flexure and extensor 19%, 3/16 Face only 31%, 5/16 Flexure only 0%, 0/16 Extensor only 0%, 0/16 Other 50%, 8/16 12-23 months (n = 9) Face, flexure and extensor 44%, 4/9 Face only 11%, 1/9 Flexure only 11%, 1/9 Extensor only 0%, 0/9 Other 33%, 3/9 > 23 months (n = 29) Face, flexure and extensor 48%, 14/29 Face only 0%, 0/29 Flexure only 10%, 3/29 Extensor only 3%, 1/29 Other 38%, 11/29	

Studies evaluating the diagnostic accuracy of atopy patch tests, skin prick tests and specific IgE levels compared to DBPCFC

Cow's milk

Diagnostic accuracy of an atopy patch test compared to a DBPCFC for detection of cow's milk allergy

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Isolauri 1996[161] EL=DS III	183 children aged 2-36 months with atopic eczema, not selected on basis of suspected allergy to cow's milk, although 'most' excluded egg from their diet.	54% on DB (and open) challenge 0 for placebo challenge	49%	51%	NR	61 (59 on open challenge)	81 (83 on open challenge)	NR	NR	No cow's milk taken 1 month before test (they were breastfed (11%), or given soya milk 39%, whey formula 24%, or amino-acid formula 26%). Antihistamines discontinued for 3 days-6 weeks before test. It is not stated whether the eczema was clear/controlled before the test Food challenges: Placebo: amino-acid derived substitute (Neocate). Test preparation: same as placebo + skimmed cow milk powder. 1-week challenge period; follow-up at weeks 1 and 2. A positive reaction to the food challenge was defined as an 'unequivocal adverse reaction to challenge' Humidified skimmed cow milk used for patch testing; left under occlusion for 48 hours and read 15 minutes after removing the patch, and at 72 hours. Reactions classified into four groups (negative, irritation, significant erythema, and erythema with oedema or eczema). Subsequent open challenge showed a 1% false negative of DB challenge.

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
										It is unclear whether food challenge was done blind to the results of the patch test. Unknown whether the sensitivity and specificity data represent those who had either or both immediate or delayed reactions
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	47 (any reaction)	96 (any reaction)	95 (any reaction)	51 (any reaction)	Antihistamines discontinued 72 hours before test. TCS (hydrocortisone 1% or betamethasone 0.1%) were permitted twice daily. It is not stated whether the eczema was clear/controlled before the test
						26 (immediate reaction)	96 (immediate reaction)	88 (immediate reaction)	56 (immediate reaction)	Food challenges: Placebo: amino-acid derived substitute (Neocate). Test preparation: 173 food challenges were undertaken; 41% with cow's milk, 24% with hen's egg, 20% with wheat and 15% with soya. Successive, increasing, doses of these foods were administered every 20 minutes. Challenges were stopped if clinical symptoms were observed or the maximum dose had been reached. Children were observed for 48 hours as inpatients. A positive reaction to the food challenge was noted if one of the following occurred: urticaria, angioedema, wheezing, vomiting, diarrhoea, abdominal pain, shock, or exacerbation of eczema. An early reaction was that occurring within 2 hours, and a delayed reaction occurred after 2 hours. Patch test: one drop fresh cow's milk, whisked egg (white and yolk), wheat powder, and soya milk. Site checked for immediate reactions after 20 minutes, then left under occlusion for 48 hours and read 20 minutes after removing the patch, and at 72 hours. A positive reaction was defined as erythema with infiltration. Irritant reactions (sharply defined brownish erythema, decrescendo phenomenon, blistering and lack of clear infiltration) were regarded as negative. It is unclear whether food challenge was done blind to the results of the other tests.
						78 (delayed reaction)	96 (delayed reaction)	93 (delayed reaction)	86 (delayed reaction)	

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Mehl 2006[181]	437 consecutive referrals for suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	49% (n=341) (DB and open challenge)				31	95	86	60	Open challenges were allowed in children <1 year with history of immediate-type reactions. 77% of challenges were double blind. >1 week elimination diet required before provocation Eczema was clear before testing. Hydrocortisone (1%) or betamethasone (0.01%) permitted twice daily. Advice to stop antihistamines 72 hours before provocation.

NR=not reported

Diagnostic accuracy of a skin prick test compared to a DBPCFC for detection of cow's milk allergy

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Isolauri 1996[161] EL= DS III	183 children aged 2-36 months with atopic eczema, not selected on basis of suspected allergy to cow's milk, although 'most' excluded egg from their diet.	54% on DB (and open) challenge 0 for placebo challenge	49%	51%	NR	48 (47 on open challenge)	86 (83 on open challenge)	NR	NR	*See atopy patch test* Commercially available cow milk allergen used for prick testing, and histamine as positive control. Reactions read at 15 mins. The test was positive if it was half the size of the histamine reaction. Unknown whether the sensitivity and specificity data represent those who had either or both immediate or delayed reactions
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	78 (any reaction)	69 (any reaction)	81 (any reaction)	64 (any reaction)	*See atopy patch test* Fresh foods were applied to the volar forearm; fresh cow's milk, whisked egg (white and yolk), wheat powder, and soya milk. A 1mm lancet was used to undertake the skin prick test. Reactions were read at 15 minutes. A wheal size of 3mm or greater, without reaction of the negative control (sodium chloride 0.9%), indicated a positive test. (Histamine dihydrochloride was used as a positive control.)
						78 (immediate reaction)	69 (immediate reaction)	72 (immediate reaction)	75 (immediate reaction)	
						78 (delayed reaction)	69 (delayed reaction)	64 (delayed reaction)	82 (delayed reaction)	
Sampson 1997[167] EL=DS III Related (earlier) publication (including 40 of the children, Sampson 1984[168])	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis. It is not clear whether all were suspected of	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish) (placebo challenge results NR)	100%*	NR	NR	96	51	66	93	It was not stated whether other treatments were permitted or discontinued, nor whether the eczema was clear/controlled before the test. Food challenges: DBPCFC were undertaken if history or skin testing suggested food hypersensitivity, otherwise open food challenge was used. Placebo: not stated Test preparation: foods used were egg, milk, peanut, wheat, soya, fish, and other foods suspected of provoking skin symptoms. Up to 10g of dehydrated food was camouflaged in juice, infant formula, or moist food, and administered over 90 minutes. A placebo and an

Study	Population tested	Prevalence	Diagnostic accuracy for cow's milk							Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
	having food allergy, but some were based on the comments made regarding use of DB and open food challenges.									active challenge were performed on the same day, 4 hours apart. All negative challenges were confirmed by open challenge. DBPCFC was not undertaken if there was a 'convincing' history of a severe allergic reaction to food (an immediate allergic reaction that developed after isolated ingestion of that food and required emergency treatment within the previous 2 years). The duration of observation was not stated, nor the characteristics of a positive test. Skin prick test: glycerinated food extracts and appropriate positive (histamine) and negative (saline) controls were applied. It was no stated when the reactions were read. A wheal size of 3mm or greater than the negative control indicated a positive test. It is unclear whether food challenge was done blind to the results of the other tests. *It seems that the accuracy of the tests for immediate reactions is considered only because all reactions developed within minutes to 2 hours of the food challenge.
Vierrucci 1989[542] EL=DS III	35 children aged 0-5 years with atopic eczema	58% (65% milk, 67% egg, 22% tomato, 56% peanut)	NR	NR	NR	28	80	66	44	Antihistamines were discontinued 7 days before the test, TCS 4-5 days before, and oral corticosteroids 10-14 days before. An exclusion diet was used (excluding up to six suspected allergens) for 1-2 weeks before the test. It was not stated whether eczema was clear/controlled before the test. Food challenges 59 were undertaken Placebo – not stated Test: cow's milk, egg, tomato, wheat. Dehydrates food mixed with water or soya milk – up to 8g given in a 1-hour period. Two challenges were administered 4 hours apart (one active, one placebo). It was not reported what constituted a positive /immediate/delayed reaction. Skin prick test: to nine foods, including cow's milk, egg, tomato, wheat and to inhalant allergens including house dust mite (all were glycerinated extracts). Positive (histamine) and negative (glycerol-saline) controls were also applied. Reactions were read at 15-20 minutes. A wheal size of 3mm or greater than the positive control was considered a positive reaction. Total and specific IgE levels were taken in some children

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
										(proportions unclear). The criteria for a positive test were not reported; therefore the diagnostic accuracy data reported in the paper for IgE are not reproduced here.
Van Bever 1989[170] EL=DS III	25 children aged 5 moths to 14 years (mean 3.5 ears) with severe atopic eczema, persistent for several months and unresponsive to topical treatments and antihistamines. Any history of food allergy was not considered in the selection of children for testing. 'Virtually all' had undergone elimination diets	47%	47%	NR	NR	43	75	60	60	All were hospitalised and given an elemental diet for 1-2 weeks. Topical treatment for eczema continued. Antihistamines were stopped for 1 week before food challenge testing. 19 were challenged with foods (milk, soya, egg, wheat), 5 with foods and food additives, and 1 with food additives only. DBPCFC (n=96)– 2 challenges were given daily, and children assessed 4 hours later. Therefore results are for immediate reactions only. Skin prick tests were performed with buffer solution (negative control), histamine, codeine, egg and milk. Wheal reactions 3mm greater than the negative control were considered positive. Specific IgE levels were also measured and diagnostic accuracy data quoted, however the threshold indicative of a positive test was not stated.
Mehl 2006[181]	437 consecutive referrals for suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	49% (n=341) (DB and open challenge)	NR	NR	NR	85	70	73	83	Open challenges were allowed in children <1 year with history of immediate-type reactions. 77% of challenges were double blind. >1 week elimination diet required before provocation Eczema was clear before testing. Hydrocortisone (1%) or betamethasone (0.01%) permitted twice daily. Advice to stop antihistamines 72 hours before provocation.

NR=not reported

Diagnostic accuracy of specific IgE compared to a DBPCFC for detection of cow's milk allergy

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	84 (any reaction) 85 (immediate reaction) *22 83 (delayed reaction) *17	38 (any reaction) 38 (immediate reaction) *96 38 (delayed reaction) *96	70 (any reaction) 59 (immediate reaction) *86 48 (delayed reaction) *75	59 (any reaction) 71 (immediate reaction) *54 77 (delayed reaction) *63	*See atopy patch test* The Pharmacia CAP system was used to measure total and specific IgE levels to cow's milk, hen's egg, wheat, and soya (detection limit 35 kU/l). Children were regarded as sensitised if their IgE levels were above the detection limit. *IgE results for a cut off of 17.5kU/L
Niggemann 1999[166] EL=DS II	107 children aged 5 months to 12 years with persistent moderate-severe atopic eczema, and suspected food-related worsening of eczema or immediate-type clinical reactions by parents and/or referring doctor. 'usual' treatments had been used, and 'no specific diets had been tried in the vast majority of children' (no further details)	51% (51% milk, 70% egg, 44% wheat, 16% soya) (placebo challenge results NR)	70% (64% of milk challenges, 82% of egg, 47% of wheat, 57% of soya) Of 89% of early reactions manifest as skin reactions, 58% were manifest as eczema, and 23% as combined eczema and urticaria	25% (28% of milk challenges, 16% of egg, 47% of wheat, 43% of soya) Of 89% of delayed reactions manifest as skin reactions, 76% were manifest as eczema, and 10% as combined eczema and urticaria	5% (8% of milk challenges, 2% of egg, 6% of wheat, 0% of soya) Of 92% of combined reactions manifest as skin reactions, 83% were manifest as eczema, and 17% as combined eczema and urticaria	85	38	61	71	For at least 5 days before challenge testing children were given a diet of either extensively hydrolysed casein formula (infants and young children) or a few foods diet (older children). Antihistamines discontinued 72 hours before test. TCS were permitted twice daily (betamethasone 0.01%). It is not stated whether the eczema was clear/controlled before the test Food challenges: Placebo: casein hydrolysate banana flavour solution (128 placebo challenges were undertaken) Test preparation: 259 food challenges were undertaken, using successive doses of fresh pasteurised cow's milk containing ultraheated soya milk or fat, raw hen's egg (white and yolk), and wheat powder. The interval between foods was 30 minutes. 'In general' two active and one placebo challenge were administered to each child. Challenges were stopped if clinical symptoms were observed or the maximum dose had been reached. Children were observed for 48 hours as inpatients. A positive reaction to the food challenge was noted if one of the following occurred: urticaria, angioedema, wheezing, vomiting, diarrhoea, abdominal pain, or exacerbation of eczema. An early reaction was that occurring within 2 hours, and a delayed reaction

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
										occurred after 2 hours. The Pharmacia CAP system was used to measure total and specific IgE levels to cow's milk, hen's egg, wheat, and soya (detection limit 35 kU/l). Children were regarded as sensitised if their IgE levels were above the detection limit. The sequence used to test the foods was determined by the dietician who was not involved in assessing the clinical status of the children during the challenges. It is assumed that the diagnostic accuracy data refer to any positive test (immediate or delayed response). The diagnostic accuracy of the history of any food related symptoms was also reported: sensitivity 48% (64% for cow's milk, 45% egg, 33% wheat, 0 soya) and specificity 72% (100% soy, 74% wheat, 58% milk, 54% egg).
Sampson 1997[167] EL=DS III Related (earlier) publication (including 40 of the children, Sampson 1984[168])	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis. It is not clear whether all were suspected of having food allergy, but some were based on the comments made regarding use of DB and open food challenges.	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish)	100%*	NR	NR	100	30	57	100	*See skin prick test.* The Pharmacia CAP system was used to measure total and specific IgE levels to egg, milk, peanut, wheat, soya, fish. 75% were also tested for inhalant allergens (house dust mite, and cat and dog dander). The detection limit was 35 kU/l; children were regarded as sensitised if their IgE levels were above the detection limit. The authors also noted that there was no correlation between the level of food allergen-specific IgE and the severity of the allergic reaction. The authors also investigated the IgE levels that would give 90% and 95% predictive values for each of the six foods tested. [those thresholds giving the most complete results quoted here] For PPV, the 95% values were: Egg 6kU/L Milk 32 kU/L Peanut 15 kU/L Fish 20 kU/L (i.e. if a child has a IgE level to fish of 20 or more, they are 95% likely to have a positive reaction on food

Study	Population tested	Prevalence	Diagnostic accuracy for cow's milk							Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
										challenge). [90% or 95% values not possible for soya or wheat] For NPV the 90% values were: Egg 0.6kU/L Milk 1.0 kU/L Peanut [not possible] Fish 5 kU/L (0.9kU/L at 95% value) Soya 5 kU/L (2 at 95% value) Wheat 79 kU/L (5 at 95% value) i.e. if a child has a IgE level to wheat of 79 or less, they are 99% likely *not* to have a positive reaction on food challenge).
Mehl 2006[181] EL=DS III	437 consecutive referrals for suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	49% (n=341) (DB and open challenge)	NR	NR	NR	87	49	62	79	Open challenges were allowed in children <1 year with history of immediate-type reactions. 77% of challenges were double blind. >1 week elimination diet required before provocation Eczema was clear before testing. Hydrocortisone (1%) or betamethasone (0.01%) permitted twice daily. Advice to stop antihistamines 72 hours before provocation

NR=not reported

Egg

Diagnostic accuracy of an atopy patch test compared to a DBPCFC for detection of egg allergy

Study	Population tested	Prevalence				Diagnostic accuracy for egg				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate, and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	57 (any reaction)	93 (any reaction)	94 (any reaction)	52 (any reaction)	
						44 (immediate reaction)	93 (immediate reaction)	89 (immediate reaction)	57 (immediate reaction)	
						80 (delayed reaction)	93 (delayed reaction)	89 (delayed reaction)	87 (delayed reaction)	
Mehl 2006[181] EL=DS III	437 consecutive referrals for suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	66% (n=193) (DB and open challenge)	NR	NR	NR	41	87	86	43	

NR=not reported

Diagnostic accuracy of a skin prick test compared to a DBPCFC for detection of egg allergy

Study	Population tested	Prevalence				Diagnostic accuracy for egg				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate, and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	89 (any reaction)	57 (any reaction)	81 (any reaction)	73 (any reaction)	
						89 (immediate reaction)	57 (immediate reaction)	73 (immediate reaction)	80 (immediate reaction)	
						90 (delayed reaction)	57 (delayed reaction)	60 (delayed reaction)	89 (delayed reaction)	
Sampson 1997[167] EL=DS III Related (earlier) publication (including 40 of the children, Sampson 1984[168])	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis. It is not clear whether all were suspected of having food allergy, but some were based on the comments made regarding use of DB and open food challenges.	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish)	100%*	NR	NR	98	53	85	90	
Vierrucci 1989[542] EL=DS III	35 children aged 0-5 years with atopic eczema	58% (65% milk, 67% egg, 22% tomato, 56% peanut)	NR	NR	NR	100	25	60	75	
Van Bever 1989[170] EL=DS III	25 children aged 5 moths to 14 years (mean 3.5 ears) with severe atopic eczema, persistent for several months and unresponsive to topical treatments and antihistamines. Any history of food allergy was not was not considered in the selection of children for testing. 'Virtually all' had undergone elimination diets	47%	47%	NR	NR	25	100	100	36	
Mehl 2006[181]	437 consecutive referrals for	66% (n=193)	NR	NR	NR	93	54	79	81	

Study	Population tested	Prevalence				Diagnostic accuracy for egg				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
EL=DS III	suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	(DB and open challenge)								

NR=not reported

Diagnostic accuracy of IgE compared to a DBPCFC for detection of egg allergy

Study	Population tested	Prevalence				Diagnostic accuracy for egg				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate, and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	96 (any reaction) 94 (immediate reaction) *28 100 (delayed reaction) *20	36 (any reaction) 36 (immediate reaction) *100 38 (delayed reaction) *100	75 (any reaction) 65 (immediate reaction) *100 53 (delayed reaction) *100	83 (any reaction) 83 (immediate reaction) *52 100 (delayed reaction) *64	*IgE results for a cut off of 17.5kU/L were also reported
Niggemann 1999[166] EL=DS II	107 children aged 5 months to 12 years with persistent moderate-severe atopic eczema, and suspected food-related worsening of eczema or immediate-type clinical reactions by parents and/or referring doctor. 'usual' treatments had been used, and 'no specific diets had been tried in the vast majority of children' (no further details)	51% (51% milk, 70% egg, 44% wheat, 16% soya) (placebo challenge results NR)	70% (64% of milk challenges, 82% of egg, 47% of wheat, 57% of soya) Of 89% of early reactions manifest as skin reactions, 58% were manifest as eczema, and 23% as combined eczema and urticaria	25% (28% of milk challenges, 16% of egg, 47% of wheat, 43% of soya) Of 89% of delayed reactions manifest as skin reactions, 76% were manifest as eczema, and 10% as combined eczema and urticaria	5% (8% of milk challenges, 2% of egg, 6% of wheat, 0% of soya) Of 92% of combined reactions manifest as skin reactions, 83% were manifest as eczema, and 17% as combined eczema and urticaria	95	38	79	75	*See cow's milk*
Sampson 1997[167] EL=DS III Related (earlier) publication (including 40 of	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis. It is not clear whether all were suspected of having	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish)	100%*	NR	NR	98	45	84	88	

Study	Population tested	Prevalence				Diagnostic accuracy for egg				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
the children, Sampson 1984[168])	food allergy, but some were based on the comments made regarding use of DB and open food challenges.									
Mehl 2006[181] EL=DS III	437 consecutive referrals for suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	66% (n=193) (DB and open challenge)	NR	NR	NR	96	48	79	85	

NR=not reported

Fish

Diagnostic accuracy of an atopy patch test compared to a DBPCFC for detection of fish allergy

No studies

Diagnostic accuracy of a skin prick test compared to a DBPCFC for detection of fish allergy

Study	Population tested	Prevalence	Diagnostic accuracy for fish							Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Sampson 1997[167] EL=DS III	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis.	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish)	100%*	NR	NR	90	57	77	80	
Related (earlier) publication (including 40 of the children, Sampson 1984[168])	It is not clear whether all were suspected of having food allergy, but some were based on the comments made regarding use of DB and open food challenges.									

NR=not reported

Diagnostic accuracy of IgE compared to a DBPCFC for detection of fish allergy

Study	Population tested	Prevalence				Diagnostic accuracy for fish				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Sampson 1997[167] EL=DS III Related (earlier) publication (including 40 of the children, Sampson 1984[168])	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis. It is not clear whether all were suspected of having food allergy, but some were based on the comments made regarding use of DB and open food challenges.	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish)	100%*	NR	NR	94	65	49	97	

NR=not reported

Peanut

Diagnostic accuracy of an atopy patch test compared to a DBPCFC for detection of peanut allergy

No studies

Diagnostic accuracy of a skin prick test compared to a DBPCFC for detection of peanut allergy

Study	Population tested	Prevalence				Diagnostic accuracy for peanut				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Sampson 1997[167] EL=DS III Related (earlier) publication (including 40 of the children, Sampson 1984[168])	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis. It is not clear whether all were suspected of having food allergy, but some were based on the comments made regarding use of DB and open food challenges.	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish)	100%*	NR	NR	90	29	55	75	
Vierrucci 1989[542] EL=DS III	35 children aged 0-5 years with atopic eczema	58% (65% milk, 67% egg, 22% tomato, 56% peanut)	NR	NR	NR	100	50	83	50	

NR=not reported

Diagnostic accuracy of IgE compared to a DBPCFC for detection of peanut allergy

Study	Population tested	Prevalence				Diagnostic accuracy for peanut				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Sampson 1997[167] EL=DS III Related (earlier) publication (including 40 of the children, Sampson 1984[168])	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis. It is not clear whether all were suspected of having food allergy, but some were based on the comments made regarding use of DB and open food challenges.	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish)	100%*	NR	NR	97	38	78	85	

NR=not reported

Soya

Diagnostic accuracy of an atopy patch test compared to a DBPCFC for detection of soya allergy

Study	Population tested	Prevalence				Diagnostic accuracy for soya				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate, and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	75	86	50	95	Results shown are for any reaction (immediate or delayed)
Mehl 2006[181] EL=DS III	437 consecutive referrals for suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	26% (n=180) (DB and open challenge)	NR	NR	NR	23	86	30	82	

NR=not reported

Diagnostic accuracy of a skin prick test compared to a DBPCFC for detection of soya allergy

Study	Population tested	Prevalence				Diagnostic accuracy for soya				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate, and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	50	90	50	90	Results shown are for any reaction (immediate or delayed)
Sampson 1997[167] EL=DS III Related (earlier) publication (including 40 of the children, Sampson 1984[168])	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis. It is not clear whether all were suspected of having food allergy, but some were based on the comments made regarding use of DB and open food challenges.	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish)	100%*	NR	NR	76	47	35	84	
Mehl 2006[181] EL=DS III	437 consecutive referrals for suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	26% (n=180) (DB and open challenge)	NR	NR	NR	29	85	33	82	

NR=not reported

Diagnostic accuracy of IgE compared to a DBPCFC for detection of soya allergy

Study	Population tested	Prevalence				Diagnostic accuracy for soya				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate, and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	75	52	23	92	Results shown are for any reaction (immediate or delayed)
Niggemann 1999[166] EL=DS II	107 children aged 5 months to 12 years with persistent moderate-severe atopic eczema, and suspected food-related worsening of eczema or immediate-type clinical reactions by parents and/or referring doctor. 'usual' treatments had been used, and 'no specific diets had been tried in the vast majority of children' (no further details)	51% (51% milk, 70% egg, 44% wheat, 16% soya) (placebo challenge results NR)	70% (64% of milk challenges, 82% of egg, 47% of wheat, 57% of soya) Of 89% of early reactions manifest as skin reactions, 58% were manifest as eczema, and 23% as combined eczema and urticaria	25% (28% of milk challenges, 16% of egg, 47% of wheat, 43% of soya) Of 89% of delayed reactions manifest as skin reactions, 76% were manifest as eczema, and 10% as combined eczema and urticaria	5% (8% of milk challenges, 2% of egg, 6% of wheat, 0% of soya) Of 92% of combined reactions manifest as skin reactions, 83% were manifest as eczema, and 17% as combined eczema and urticaria	100	26	23	100	*See cow's milk*
Sampson 1997[167] EL=DS III Related (earlier) publication (including 40 of the children,	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis. It is not clear whether all were suspected of having food allergy, but some were based on the comments made	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish)	100%*	NR	NR	94	25	21	95	

Study	Population tested	Prevalence				Diagnostic accuracy for soya				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Sampson 1984[168])	regarding use of DB and open food challenges.									
Mehl 2006[181] EL=DS III	437 consecutive referrals for suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	26% (n=180) (DB and open challenge)	NR	NR	NR	65	50	22	86	

NR=not reported

Wheat

Diagnostic accuracy of an atopy patch test compared to a DBPCFC for detection of wheat allergy

Study	Population tested	Prevalence				Diagnostic accuracy for wheat				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Majamaa 1999[162] EL=DS II	39 children aged under 2 years who were suspected of having wheat allergy; 36 had atopic eczema	56% overall (67% of the DB challenges, and 40% of the open challenges) 0 for placebo challenge	23% (of the positive DB challenges)	77% (of the positive DB challenges, of which 6/17 were atopic eczema, and 10/17 both atopic eczema and gastrointestinal symptoms, 1/17 had diarrhoea)	NR	86 (95% CI 65, 97)*	35 (95% CI 14, 62)*	63 (95% CI 44, 80)*	67 (95% CI 30, 93)*	Antihistamines discontinued for 3 days-6 weeks before test. It is not stated whether the eczema was clear/controlled before the test. A cereal-elimination diet was used for at least 3-4 weeks. Children with delayed-type reactions were primarily challenged in the double-blind challenge (n=24), and those with immediate type reactions in an open challenge (n=15). Placebo: amino-acid derived substitute (Neocate). Test preparation: same as placebo + wheat flour in water. 1-week challenge period; follow-up at weeks 1 and 2. A positive reaction was not defined. For patch testing a porridge was made of saline, milk powder, lyophilised egg white, wheat, barley, rye, oats, and soya flour. This was left under occlusion for 48 hours and read 15 minutes after removing the patch, and at 72 hours. A negative reaction was defined as no visible or palpable change on the skin, and a positive test as clear redness with palpable infiltration. It is unclear whether food challenge was done blind to the results of the other tests. Unknown whether the sensitivity and specificity data represent those who had either or both immediate or delayed reactions. *Results were presented for all children, that is data for both open and DB challenges were only reported as

Study	Population tested	Prevalence				Diagnostic accuracy for wheat				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
										combined data.
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate, and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	89	94	94	89	Results shown are for any reaction (immediate or delayed)
Mehl 2006[181] EL=DS III	437 consecutive referrals for suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	36% (n=159) (DB and open challenge)	NR	NR	NR	27	89	58	69	

NR=not reported

Diagnostic accuracy of a skin prick test compared to a DBPCFC for detection of wheat allergy

Study	Population tested	Prevalence				Diagnostic accuracy for wheat				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Majamaa 1999[162] EL=DS II	39 children aged under 2 years who were suspected of having wheat allergy; 36 had atopic eczema	56% overall (67% of the DB challenges, and 40% of the open challenges) 0 for placebo challenge	23% (of the positive DB challenges)	77% (of the positive DB challenges, of which 6/17 were atopic eczema, and 10/17 both atopic eczema and gastrointestinal symptoms, 1/17 had diarrhoea)	NR	23 (95% CI 9, 46)*	100 (95% CI 80, 99)*	100 (95% CI 48, 98)*	50 (95% CI 33, 68)*	*See atopy patch test table for more study details.* Commercially available cow's milk, egg, fish, soya, pea allergens, 200mg of cereal flours, and soya flour diluted in saline for prick testing. Histamine was the positive control. Reactions read at 15 minutes. The test was positive if the mean diameter of the wheal was at least 3mm and the negative control (not specified) was 0 at the same time. *Results were presented for all children, that is data for both open and DB challenges were only reported as combined data.
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate, and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	67	53	60	60	Results shown are for any reaction (immediate or delayed)
Sampson 1997[167] EL=DS III Related (earlier) publication (including 40 of the children, Sampson 1984[168])	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis. It is not clear whether all were suspected of having food allergy, but some were based on the comments made regarding use of DB and open food challenges.	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish)	100%*	NR	NR	90	51	35	94	

Study	Population tested	Prevalence				Diagnostic accuracy for wheat				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Mehl 2006[181] EL=DS III	437 consecutive referrals for suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	36% (n=159) (DB and open challenge	NR	NR	NR	75	64	49	85	

NR=not reported

Diagnostic accuracy of IgE compared to a DBPCFC for detection of wheat allergy

Study	Population tested	Prevalence				Diagnostic accuracy for wheat				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Majamaa 1999[162] EL=DS II	39 children aged under 2 years who were suspected of having wheat allergy; 36 had atopic eczema	56% overall (67% of the DB challenges, and 40% of the open challenges) 0 for placebo challenge	23% (of the positive DB challenges)	77% (of the positive DB challenges, of which 6/17 were atopic eczema, and 10/17 both atopic eczema and gastrointestinal symptoms, 1/17 had diarrhoea)	NR	20 (95% CI 7, 44)*	93 (95% CI 66, 100)*	80 (95% CI 28, 99)*	45 (95% CI 26, 64)*	*See atopy patch test table for more study details.* A positive IgE level (using a RAST assay) was not defined. It was reported that an elevated wheat-specific IgE level was seen in 20% of those with challenge-proven wheat allergy (levels 0.7-6.5 kU/l). *Results were presented for all children, that is data for both open and DB challenges were only reported as combined data.
Roehr 2001[165] EL=DS III	98 children aged 2 months to 11.2 years with atopic eczema (62% mild, 28% moderate, and 10% severe). Not stated whether they were suspected of having food allergy.	55% (64% milk, 67% egg, 51% wheat, 16% soya) (placebo challenge results NR)	49%	26% All atopic eczema	25% All atopic eczema plus respiratory or gastrointestinal symptoms	67	47	57	57	Results shown are for any reaction (immediate or delayed)
Niggemann 1999[166] EL=DS II	107 children aged 5 months to 12 years with persistent moderate-severe atopic eczema, and suspected food-related worsening of eczema or immediate-type clinical reactions by parents and/or referring doctor. 'usual' treatments had been used, and 'no specific diets had been tried in the vast majority of children' (no further details)	51% (51% milk, 70% egg, 44% wheat, 16% soya) (placebo challenge results NR)	70% (64% of milk challenges, 82% of egg, 47% of wheat, 57% of soya) Of 89% of early reactions manifest as skin reactions, 58% were manifest as eczema, and 23% as combined	25% (28% of milk challenges, 16% of egg, 47% of wheat, 43% of soya) Of 89% of delayed reactions manifest as skin reactions, 76% were manifest as eczema, and 10% as combined eczema and urticaria	5% (8% of milk challenges, 2% of egg, 6% of wheat, 0% of soya) Of 92% of combined reactions manifest as skin reactions, 83% were manifest as eczema, and 17% as combined eczema and urticaria	80	6	43	25	*See cow's milk*

Study	Population tested	Prevalence				Diagnostic accuracy for wheat				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
			eczema and urticaria							
Sampson 1997[167] EL=DS III Related (earlier) publication (including 40 of the children, Sampson 1984[168])	196 children and adolescents, aged 0.6-17.9 years with atopic eczema, 'approximately' 50% of whom also had asthma and allergic rhinitis. It is not clear whether all were suspected of having food allergy, but some were based on the comments made regarding use of DB and open food challenges.	46% (50% to milk, 73% egg, 49% peanut, 28% soya, 22% wheat, 55% fish)	100%*	NR	NR	96	20	14	97	
Mehl 2006[181] EL=DS III	437 consecutive referrals for suspected food allergy. Children aged 3 months – 14 years (median=13 months). 90% had AE	36% (n=159) (DB and open challenge)	NR	NR	NR	82	34	41	77	

NR=not reported

Tomato

Diagnostic accuracy of an atopy patch test compared to a DBPCFC for detection of tomato allergy

No studies

Diagnostic accuracy of a skin prick test compared to a DBPCFC for detection of tomato allergy

Study	Population tested	Prevalence				Diagnostic accuracy for tomato				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Vierrucci 1989[542] EL=DS III	35 children aged 0-5 years with atopic eczema	58% (65% milk, 67% egg, 22% tomato, 56% peanut)	NR	NR	NR	100	66	40	100	

NR=not reported

Diagnostic accuracy of IgE compared to a DBPCFC for detection of tomato allergy

No studies

Studies for which a range of allergens were tested but accuracy data not reported for each allergen separately

Study	Population tested	Prevalence				Diagnostic accuracy for various food allergens				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Niggemann 2000[163] EL=DS II (Related publication Niggemann 2002[164]	75 children aged 4 months-12.5 year with suspected food-related symptoms; 69 (92%) had atopic eczema. During their hospital stay they were on an exclusion diet of extensively hydrolysed casein formula, or an amino-acid based formula.	58% of the DB challenges (66% of those tested with egg, 65% cow's milk, 48% wheat, 27% soya) 2.6% for placebo challenges	51%	27% (all were exacerbations of eczema)	22% (all included exacerbations of eczema)	Atopy patch test: 55 (any reaction)	Atopy patch test: 95 (any reaction)	Atopy patch test: 93 (any reaction)	Atopy patch test: 60 (any reaction)	'when necessary ' skin was cleared before (no further details) 209 oral challenges were undertaken with children as hospital inpatients. The food allergens tested were hen's egg, cow's milk, wheat, soya. The clinician undertaking the test was blind to the results of skin testing and IgE. Placebo: amino-acid derived substitute (Neocate). Tests preparation: every 48 hours successive doses of fresh pasteurised cow's milk (containing soyabean milk), raw hen's egg, and wheat powder were given. Provocation was stopped if symptoms appeared or if the maximum dose was reached. Test positive if clinical reactions observed such as urticaria, angioedema, wheezing, vomiting, diarrhoea, or exacerbation of eczema (defined as an increase in SCORAD score of 10 points or more). Antihistamines were withdrawn at least 3 days before testing. TCS were allowed twice a day (hydrocortisone 1% or betametasone valerate 0.3% twice daily, but not 48 hours before patch testing). Atopy patch test: cow's milk, hen's egg, wheat, soyabean milk; occlusion for 48 hours, results read after 20 minutes and again at 72 hours. Positive test if erythema plus clear infiltration occurred. Skin prick test: cow's milk, hen's egg, wheat, soyabean milk; reactions read at 15 minutes, positive if the wheal was 3mm or more without reaction of negative control (not specified). Histamine was used as the positive control. IgE (specific to cow's milk, egg, wheat and soya) measured using the CAP system; positive if the level was higher than 0.35 kU/l.
						33 (immediate reaction)	95 (immediate reaction)	81 (immediate reaction)	67 (immediate reaction)	
						76 (delayed reaction)	95 (delayed reaction)	81 (delayed reaction)	93 (delayed reaction)	
						Skin prick test: 83 (any reaction)	Skin prick test: 70 (any reaction)	Skin prick test: 79 (any reaction)	Skin prick test: 75 (any reaction)	
						95 (immediate reaction)	70 (immediate reaction)	69 (immediate reaction)	95 (immediate reaction)	
						58 (delayed reaction)	70 (delayed reaction)	41 (delayed reaction)	81 (delayed reaction)	
						IgE: 86 (any reaction)	IgE: 29 (any reaction)	IgE: 62 (any reaction)	IgE: 59 (any reaction)	
						95 (immediate reaction)	29 (immediate	62 (immediate	59 (immediate	

Study	Population tested	Prevalence				Diagnostic accuracy for various food allergens				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
							reaction)	reaction)	reaction)	
						71 (delayed reaction)	29 (delayed reaction)	37 (delayed reaction)	72 (delayed reaction)	
Niggemann 1999[166] EL=DS II	107 children aged 5 months to 12 years with persistent moderate-severe atopic eczema, and suspected food-related worsening of eczema or immediate-type clinical reactions by parents and/or referring doctor. 'usual' treatments had been used, and 'no specific diets had been tried in the vast majority of children' (no further details)	51% (51% milk, 70% egg, 44% wheat, 16% soya) (placebo challenge results NR)	70% (64% of milk challenges, 82% of egg, 47% of wheat, 57% of soya) Of 89% of early reactions manifest as skin reactions, 58% were manifest as eczema, and 23% as combined eczema and urticaria	25% (28% of milk challenges, 16% of egg, 47% of wheat, 43% of soya) Of 89% of delayed reactions manifest as skin reactions, 76% were manifest as eczema, and 10% as combined eczema and urticaria	5% (8% of milk challenges, 2% of egg, 6% of wheat, 0% of soya) Of 92% of combined reactions manifest as skin reactions, 83% were manifest as eczema, and 17% as combined eczema and urticaria	IgE: 90	IgE: 30	IgE: 59	IgE: 73	The diagnostic accuracy data for 'all' (assumed this means any) of the four allergens tested was reported in this study (as well as data for each allergen). The four allergens were cow's milk, hen's egg, wheat, and soya. IgE (specific to cow's milk, egg, wheat and soya) measured using the CAP system; positive if the level was higher than 0.35 kU/l. It was reported that the specificity for all (any) allergen fell with increasing age (33% for children aged 0-24 months, 29% for 25-48 months and 26% for older children) Results represent any reaction (immediate or delayed).
Breuer 2004[169]	64 children aged 1-10 years with mild to severe atopic eczema, and suspected of having food-related worsening of atopic eczema or immediate type	46% (47% to cow's milk, 62% egg, 35% wheat, 35% soya) 3.8% for placebo	43% (40% to cow's milk, 53% egg, 22% wheat, 50% soya) (86%	12% (13% to cow's milk, 5% egg, 33% wheat, 0% soya) (all delayed reactions were eczema)	45% (47% to cow's milk, 42% egg, 44% wheat, 50% soya) (all delayed reactions	Atopy patch test (APT): 70 (any reaction) APT: 67 (immediate	APT: 41 (any reaction) APT: 38 (immediate	APT: 45 (any reaction) APT: 38 (immedi	APT: 67 (any reaction) APT: 67 (immediate	Antihistamines discontinued 72 hours before test. Use of emollients and mild TCS (no further details) continued during the study. It is not stated whether the eczema was clear/controlled before the test The foods suspected of causing the food allergy were excluded from the diet for 4 weeks prior to the food challenge.

Study	Population tested	Prevalence				Diagnostic accuracy for various food allergens				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
	reactions to foods by their parents and/or referring doctor.	challenge	involved the skin only, 12% skin and respiratory tract, and 2% skin and gastrointestinal tract)		were eczema)	reaction)	reaction)	ate reaction)	reaction)	The four allergens were cow's milk, hen's egg, wheat, and soya. Food challenges: Placebo: soya hydrolysate mixed with blackcurrant flavour (Pregomin). 52 challenges were undertaken. Test preparation: 106 food challenges were undertaken, using fresh pasteurised cow's milk, egg, powder, wheat gluten, and soya milk (all mixed in soya hydrolysate with blackcurrant flavour). 33 were challenged with one food, 21 with two, 9 with three, and 1 with all four. Successive, increasing, doses of these foods were administered every 30 minutes. On the second day the full doses were given all at once. Children were observed for 48 hours. An early reaction included symptoms such as urticaria, angioedema, vomiting, rhinitis, bronchial obstruction, that occurring within 6 hours. A positive late reaction was defined as an increase of 10 SCORAD points or more, occurring after 6 hours. Patch test: using fresh pasteurised cow's milk, hen's egg powder, wheat gluten and soya milk. Test left under occlusion for 24 hours then checked 30 minutes after removing the occlusion, and 24 hours and 48 hours thereafter. A positive reaction was defined as erythema with infiltration. The Pharmacia CAP system was used to measure specific IgE levels. The detection limit was 35 kU/l; children were regarded as sensitised if their IgE levels were above the detection limit. It is unclear whether food challenge was done blind to the results of the other tests. It was reported that sensitivity, specificity, PPV and NPV were higher in children under 2 years of age (86%, 74%, 75% and 95% respectively) compared to those aged 2 or above (70%, 57%, 56% and 71% respectively)
						APT: 67 (delayed reaction)	APT: 38 (delayed reaction)	APT: 24 (delayed reaction)	APT: 79 (delayed reaction)	
						IgE: 76 (any reaction)	IgE: 63 (any reaction)	IgE: 64 (any reaction)	IgE: 75 (any reaction)	
						IgE: 77 (immediate reaction)	IgE: 60 (immediate reaction)	IgE: 57 (immediate reaction)	IgE: 79 (immediate reaction)	
						IgE: 68 (delayed reaction)	IgE: 50 (delayed reaction)	IgE: 33 (delayed reaction)	IgE: 81 (delayed reaction)	

NR=not reported

Combined data

Study	Allergen (any type of reaction)	Tests	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Isolauri 1996[161]	Cow's milk	Atopy patch + skin prick (in parallel)	86	72	NR	NR
	Cow's milk	Atopy patch + skin prick (serially)	24	94	NR	NR
Roehr 2001[165]	Cow's milk	Atopy patch + skin prick	74	100	100	74
	Cow's milk	Atopy patch + IgE	79	100	100	64
	Cow's milk	Skin prick + IgE	85	56	83	60
	Cow's milk	Atopy patch + skin prick + IgE	81	100	100	67
	Egg	Atopy patch + skin prick	84	89	94	73
	Egg	Atopy patch + IgE	94	83	94	83
	Egg	Skin prick + IgE	96	43	86	75
	Egg	Atopy patch + skin prick + IgE	94	75	94	75
	Wheat	Atopy patch + skin prick	86	90	92	82
	Wheat	Atopy patch + IgE	92	89	92	89
	Wheat	Skin prick + IgE	71	50	63	60
	Wheat	Atopy patch + skin prick + IgE	91	86	91	86
	Soy	Atopy patch + skin prick	67	100	100	94
	Soy	Atopy patch + IgE	100	83	50	100
	Soy	Skin prick + IgE	100	91	50	100
	Soy	Atopy patch + skin prick + IgE	100	100	100	100
Mehl 2006[181]	Cow's milk	Atopy patch + skin prick	69	97	92	86
	Cow's milk	Atopy patch +IgE	74	94	90	83
	Cow's milk	Atopy patch + skin prick + IgE	82	95	91	90
	Egg	Atopy patch + skin prick	85	89	92	80
	Egg	Atopy patch +IgE	91	83	91	83
	Egg	Atopy patch + skin prick + IgE	92	82	92	82
	Wheat	Atopy patch + skin prick	43	90	50	86
	Wheat	Atopy patch +IgE	62	81	65	78
	Wheat	Atopy patch + skin prick + IgE	60	85	60	85
	Soy	Atopy patch + skin prick	14	96	43	82
	Soy	Atopy patch +IgE	31	85	27	87
	Soy	Atopy patch + skin prick + IgE	20	93	33	87

Studies evaluating the diagnostic accuracy of atopy patch tests, skin prick tests and specific IgE levels compared to an open food challenge

Cow's milk

Diagnostic accuracy of an atopy patch test compared to an open food challenge for detection of cow's milk allergy

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Cudowska 2005[171] EL=DS III	34 children aged 5 months – 16 years with atopic eczema, and suspected allergy to cow's milk and/or other foods	65% in children aged under 3 years 36% in children over 3 years of age	9% (all in children under 3 years)	91% (50% in children under 3 years, 36% in children over 3 years; exacerbations of atopic eczema in 73%)	NR	80 (under 3 years of age) 80 (over 3 years of age)	70 (under 3 years of age) 89 (over 3 years of age)	73 (under 3 years of age) 80 (over 3 years of age)	22 (under 3 years of age) 11 (over 2 years of age)	Results in children under 3 years (n=20) and over 3 years of age (n=14) were compared. 75% of those under 3 years had been on a milk-free diet, vs 36% in the older than 3 years group. Antihistamines discontinued for an unspecified period before testing; TCS discontinued 48 hours before the test. Eczema was clear/controlled before the test. Food challenges: increasing amounts of milk at 30 minute intervals, after a 1-month milk-free diet. The food was blinded in children aged over 1 year (in apple pulp or rice). Immediate reactions: those within 2 hours; children assessed by parents at home at 24 hours. Challenge discontinued when a clinical reaction was noted. A positive reaction as recorded if one of the following occurred: skin eruptions, exacerbation of atopic skin lesions, oedema, urticaria, (other listed not reproduced here). Patch testing: porridge made from isotonic saline and cow's milk powder, egg white, cereals, gliadin, soy, maize rice. 8mm diameter Finn chambers used for children aged under 3 years, and 12mm for those aged over 3 years. Microcrystalline cellulose used as a negative control. Sites checked after 20 minutes for immediate reactions and then left under occlusion for 48 hours; read 15 minutes after removing the patch, and at 72 hours. Reactions classified into four groups (no reaction, redness [doubtful reaction], redness and palpable infiltration [positive], redness, infiltration and vesicles [strong positive]).

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
										Skin prick test: milk powder containing 3% fat diluted in water; whisked egg white and yolk. (SPT with soy, wheat, banana, orange, sesame, arachides, fish, beef, chicken was also undertaken to detect co-sensitisation). Sodium chloride 0.9% was the negative control, and 9% codeine the positive control. A wheal diameter of 3mm was considered a positive result. IgE: to cow's milk, egg white, soy, wheat, maize, rice using UniCAP; positive if the specific IgE level was higher than 0.70 kU/l. It is unclear whether food challenge was done blind to the results of the other tests. Results for immediate reactions to skin prick test / IgE were also reported - but it seems only in combination. The diagnostic accuracy data quoted are for delayed reactions.
Stromberg 2002[177] EL=DS III	141 children aged 2 months-4 years (mean 16 months) with atopic eczema, referred to an allergy unit for investigation	45% cow's milk, 55% egg, 43% wheat, 43% rye	13% milk, 14% egg, 3% wheat, 3% rye	87% cow's milk, 86% egg, 97% wheat, 97% rye	NR	60	97	95	75	Antihistamines discontinued 72 hours before test. It is not stated whether the eczema was clear/controlled before the test Food challenges: undertaken after a 2-week elimination diet. For nursing mothers one food was reintroduced one at a time after an interval of at least 7 days. Children who were not breastfed were given increasing amounts of food in hospital then continued at home for 1 week unless obvious symptoms were noted earlier. The definition of a positive test was not explicit. An early reaction was that occurring within 2 hours, and a delayed reaction occurred after 2 hours. Patch test: porridge of cow's milk powder, egg white, wheat or rye. Site checked for immediate reactions after 20 minutes, then left under occlusion for 48 hours and read 15 minutes after removing the patch, and at 72 hours. A positive reaction was defined as erythema with infiltration. Redness alone was regarded as negative. It is unclear whether food challenge was done blind to the results of the other tests. Skin prick tests were performed before eliminating any foods from

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
										the mother's or child's diet. They were conducted on the volar forearm, tested for low fat cow's milk, egg white, wheat and rye. Histamine was used as a positive control. Reactions were read after 15 minutes. A wheal of 3mm or more in diameter was considered positive.

NR=not reported

Diagnostic accuracy of a skin prick test compared to an open food challenge for detection of cow's milk allergy

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Cantani 1995[172] EL=DS III	146 children aged 5-48 months with atopic eczema believed to be associated with food allergy	45% (44% to milk, 47% egg, 50% other foods)	14% (to milk)	30% (to milk)	NR	83 (any reaction)	32 (any reaction)	47 (any reaction)	72 (any reaction)	It was not stated whether other treatments were permitted or discontinued before the test. Eczema was clear before the test.
						88 (immediate reaction)	28 (immediate reaction)	19 (immediate reaction)	92 (immediate reaction)	Food challenges: cow's milk or egg given in successive, increasing quantities. Immediate reaction; that occurring within 2 hours, delayed thereafter. Test continued at home, results gathered after 7-15 days. Other foods were tested (not specified). The food challenge testing was done 'independently' of the other tests, after a 4-6 week diet free of cow's milk and egg (cow's milk substitutes were given). Skin prick test: to cow's milk, egg, wheat, fish, soy, Alternaria alternate, house dust mite (no details of type of food extract). Positive (histamine) and negative (glycerol-saline) controls were also applied. Reactions were read at 20 minutes. Four grades of a reactions were noted, based on ratio of the test wheal to the histamine wheal (half, same, twice, more than twice the size). IgE: to cow's milk, egg, wheat, fish, soy, Alternaria alternate, house dust mite (no details of type of food extract), using PRSIT test. Positive if the total IgE level was higher than two SDs for the child's age. Specific IgE categorised into 4 groups (<0.35IU/ml, 0.35-0.7, 0.7-17, >17).
Stromberg 2002[177] EL=DS III	141 children aged 2 months-4 years (mean 16 months) with atopic eczema, referred to an allergy unit for investigation	45% cow's milk, 55% egg, 43% wheat, 43% rye	13% milk, 14% egg, 3% wheat, 3% rye	87% cow's milk, 86% egg, 97% wheat, 97% rye	NR	41	99	96	68	
Cantani 2006[179] EL=DS III	58 children aged 9 months-12 years with atopic eczema and food allergy (confirmed by	29% to milk, 38% to egg, 28% to wheat	NR	NR	NR	88	30	46	79	Antihistamines and TCS were stopped at least 2 weeks before testing. Food challenges: 58 were undertaken. Cow's milk, emulsified raw egg or wheat used in successive increasing

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
	elimination of foods) Control group: 60 nonatopic children									doses until any symptoms observed. Immediate – a reaction within 2 hours. The prick-prick test involves using a lancet to prick fresh foods and then immediately pricking the skin. Fresh, uncooked foods bought locally were used. The prick-prick test results were not compared to he open challenge results. Skin prick test: on volar arm. Histamine used as a positive control, isotonic saline as a negative control. A range of foods an inhalant allergens were tested. Both prick-prick and skin prick tests were read after 20 minutes – test positive if the wheal was at least twice the size of the histamine wheal (i.e. 3 mm diameter or more). The accuracy results represent any positive reaction. Diagnostic accuracy of IgE (RAST) was also reported but no information was given about IgE testing (method or definition of a positive test).

NR=not reported

Diagnostic accuracy of specific IgE compared to an open food challenge for detection of cow's milk allergy

Study	Population tested	Prevalence				Diagnostic accuracy for cow's milk				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Cantani 1995[172] EL=DS III	146 children aged 5-48 months with atopic eczema believed to be associated with food allergy	45% (44% to milk, 47% egg, 50% other foods)	14% (to milk)	30% (to milk)	NR	59 (any reaction) 71 (immediate reaction)	60 (any reaction) 56 (immediate reaction)	52 (any reaction) 24 (immediate reaction)	67 (any reaction) 91 (immediate reaction)	Unclear what a positive test was – assumed mover than 0.35 IU/ml (but 4 classes were used above this level)

NR=not reported

Egg

Diagnostic accuracy of an atopy patch test compared to an open food challenge for detection of egg allergy

Study	Population tested	Prevalence				Diagnostic accuracy for egg				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Giusti 2005[174] EL=DS III	85 children aged 6 months-14 years with atopic eczema	31% had an 'eczematous response' (no further details)	NR	NR	NR	77 (all children)	81 (all children)	65 (all children)	89 (all children)	Eczema was stable before the tests were undertaken. Food challenge: undertaken after a 3-4 week diet free of milk egg and peanuts. Cooked egg given, in hospital to start then at home. Testing stopped after a clinical reaction (cutaneous, respiratory, or gastrointestinal) was observed. All children were examined on day 7 of the challenge. Atopy patch test: a 2:1 mixture of egg yolk or white and petrolatum oil was prepared every day; 20mg was applied to the back using large (not specified) Finn chambers, for 72 hours. Results were read 30 and 60 minutes after removal of the occlusion, and graded into four categories based on presence or absence of erythema, oedema, and papules. A negative reaction was redness with no infiltration. Skin prick tests on the volar forearm with egg yolk and white using commercial allergens.
						70 (aged 6 months-2 years, n=21)	73 (aged 6 months-2 years, n=21)	70 (aged 6 months-2 years, n=21)	73 (aged 6 months-2 years, n=21)	
						75 (aged 3-6 years n=33)	80 (aged 3-6 years n=33)	55 (aged 3-6 years n=33)	91 (aged 3-6 years n=33)	
						88 (aged 7-14 years n=31)	87 (aged 7-14 years n=31)	70 (aged 7-14 years n=31)	95 (aged 7-14 years n=31)	
Stromberg 2002[177] EL=DS III	141 children aged 2 months-4 years (mean 16 months) with atopic eczema, referred to an allergy unit for investigation	45% cow's milk, 55% egg, 43% wheat, 43% rye	13% milk, 14% egg, 3% wheat, 3% rye	87% cow's milk, 86% egg, 97% wheat, 97% rye	NR	71	97	96	73	

NR=not reported

Diagnostic accuracy of a skin prick test compared to an open food challenge for detection of egg allergy

Study	Population tested	Prevalence				Diagnostic accuracy for egg				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Cantani 1995[172] EL=DS III	146 children aged 5-48 months with atopic eczema believed to be associated with food allergy	45% (44% to milk, 47% egg, 50% other foods)	20% (to egg)	27% (to egg)	2%	91 (any reaction)	32 (any reaction)	46 (any reaction)	85 (any reaction)	
						100 (immediate reaction)	28 (immediate reaction)	23 (immediate reaction)	100 (immediate reaction)	
Giusti 2005[174] EL=DS III	85 children aged 6 months-14 years with atopic eczema	31% had an 'eczematous response' (no further details)	NR	NR	NR	46 (all children)	93 (all children)	75 (all children)	80 (all children)	
						60 (aged 6 months-2 years, n=21)	100 (aged 6 months-2 years, n=21)	100 (aged 6 months-2 years, n=21)	73 (aged 6 months-2 years, n=21)	
						63 (aged 3-6 years n=33)	92 (aged 3-6 years n=33)	71 (aged 3-6 years n=33)	89 (aged 3-6 years n=33)	
						13 (aged 7-14 years n=31)	91 (aged 7-14 years n=31)	33 (aged 7-14 years n=31)	75 (aged 7-14 years n=31)	
Monti 2002[175] EL=DS III	107 children aged 1-19 months (mean 6 months) with atopic eczema who had never eaten egg (directly or indirectly). The challenges were undertaken when the children were aged 12-24 months. Atopic eczema was mild	67% (49% of those with mild eczema, 79% of those with moderate, and 80% of those with severe eczema). 17% of reactions were exacerbation of	57%	21% early, 17% late	6%	Egg white: 88 (3mm positive test) 63 (4mm positive test) 18 (5mm positive test)	Egg white: 86 (3mm positive test) 91 (4mm positive test) 100 (5mm positive test)	Egg white: 93 (3mm positive test) 94 (4mm positive test) 100 (5mm positive test)	Egg white: 77 (3mm positive test) 54 (4mm positive test) 37 (5mm positive test)	Antihistamines and corticosteroids (not stated whether topical) were stopped 15 days before testing. It was not reported whether the eczema was stable/controlled before the tests were undertaken. Food challenge: one raw egg given as a test dose. Positive reaction if clinical reactions observed (rash, urticaria, angioedema, eczema, or gastrointestinal respiratory, or ocular or cardiovascular effects). Immediate if appeared within 1 hour, early at 1-6 hours, and late after the 6th hour. Children were

Study	Population tested	Prevalence				Diagnostic accuracy for egg				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
	in 38%, moderate in 34%, and severe in 28%	eczema.				Egg yolk: 67 (3mm positive test) 26 (4mm positive test) 4 (5mm positive test)	Egg yolk: 89 (3mm positive test) 94 (4mm positive test) 100 (5mm positive test)	Egg yolk: 92 (3mm positive test) 91 (4mm positive test) 100 (5mm positive test)	Egg yolk: 56 (3mm positive test) 38 (4mm positive test) 34 (5mm positive test)	discharged after 32 hours if no reaction – they continued to ingest egg every day for 8 days. Skin prick tests on the volar forearm with egg yolk and white using commercial allergens. Histamine was used as the positive control, and a glycerol-saline solution as a negative control. Wheal size to histamine was measured after 15 minutes, and to egg after 20 minutes. Results for a wheal size of 3, 4, and 5mm were given. Specific IgE levels using CAP RAST were measured. Results read as: negative 0-35 KU/L, borderline 0.35-0.69, positive 0.7-3.49, strong positive 3.5-17.49, highly positive 17.5-49, very highly positive 50-99, extremely highly positive if >99ku/l. It is assumed that the accuracy results represent any positive reaction.
Stromberg 2002[177] EL=DS III	141 children aged 2 months-4 years (mean 16 months) with atopic eczema, referred to an allergy unit for investigation	45% cow's milk, 55% egg, 43% wheat, 43% rye	13% milk, 14% egg, 3% wheat, 3% rye	87% cow's milk, 86% egg, 97% wheat, 97% rye	NR	60	97	96	67	
Cantani 2006[179] EL=DS III	58 children aged 9 months-12 years with atopic eczema and food allergy (confirmed by elimination of foods) Control group: 60 nonatopic children	29% to milk, 38% to egg, 28% to wheat	NR	NR	NR	95	38	60	88	

NR=not reported

Diagnostic accuracy of IgE compared to an open food challenge for detection of egg allergy

Study	Population tested	Prevalence				Diagnostic accuracy for egg				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Cantani 1995[172] EL=DS III	146 children aged 5-48 months with atopic eczema believed to be associated with food allergy	45% (44% to milk, 47% egg, 50% other foods)	20% (to egg)	27% (to egg)	2%	73 (any reaction)	65 (any reaction)	57 (any reaction)	79 (any reaction)	Unclear what a positive test was – assumed mover than 0.35 IU/ml (but 4 classes were used above this level)
						90 (immediate reaction)	59 (immediate reaction)	33 (immediate reaction)	96 (immediate reaction)	
Monti 2002[175] EL=DS III	107 children aged 1-19 months (mean 6 months) with atopic eczema who had never eaten egg (directly or indirectly). The challenges were undertaken when the children were aged 12-24 months. Atopic eczema was mild in 38%, moderate in 34%, and severe in 28%	67% (49% of those with mild eczema, 79% of those with moderate, and 80% of those with severe eczema). 17% of reactions were exacerbation of eczema.	57%	21% early, 17% late	6%	If IgE >99 ku/l considered positive: 17	If IgE >99 ku/l considered positive: 100	If IgE >99 ku/l considered positive: 100	If IgE >99 ku/l considered positive: 37	It is assumed that the accuracy results represent any positive reaction.
						If IgE >17.5 ku/l considered positive: 24	If IgE >17.5 ku/l considered positive: 100	If IgE >17.5 ku/l considered positive: 100	If IgE >17.5 ku/l considered positive: 39	

NR=not reported

Peanut

Diagnostic accuracy of an atopy patch test compared to an open food challenge for detection of peanut allergy

Study	Population tested	Prevalence				Diagnostic accuracy for peanut				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Seidenari 2003[176] EL=DS III	132 children and adults aged 3-28 years (mean 12 years) with atopic eczema (33% mild, 52% moderate, 14% severe). It was not stated whether there was a history or suspicion of food allergy. None had been treated with systemic corticosteroids, antihistamines with long half-lives (not specified) or ciclosporin for 4 months prior to the study	9%	8%	50% (all eczema)	42% (all included eczema)	75 (all ages)	87 (all ages)	36 (all ages)	97 (all ages)	Antihistamines were discontinued 7 days before patch testing. Eczema was stable /controlled when testing was undertaken. Food challenge: undertaken after a 4 week diet free of milk egg and peanuts. Peanuts were given daily in increasing quantities, in hospital to start then at home for 7 days. Testing stopped after a clinical reaction (cutaneous, respiratory, or gastrointestinal) was observed. Atopy patch test: peanuts were whipped and mixed with petrolatum. 20mg of this was applied to the back using a 12mm finn chamber, and left under occlusion for 72 hours. Results were read 30-60 minutes after removal of the occlusion, and graded into four categories based on presence or absence of erythema, oedema, and papules. A negative reaction was redness and oedema with no infiltration. Skin prick tests on the volar forearm using commercial allergens (not specified). Reactions were read at 15-20 minutes; test positive if the wheal size was 3mm or more. Histamine was used as a positive control. Specific IgE was measured in 57% using the Pharmaci uniCAP system. It is assumed that the accuracy results represent any positive reaction.
						100 (under 6 years)	82 (under 6 years)	25 (under 6 years)	100 (under 6 years)	
						75 (6-12 years)	83 (6-12 years)	38 (6-12 years)	96 (6-12 years)	
						50 (older than 12 years)	94 (older than 12 years)	40 (older than 12 years)	96 (older than 12 years)	

NR=not reported

Diagnostic accuracy of a skin prick test compared to an open food challenge for detection of peanut allergy

Study	Population tested	Prevalence				Diagnostic accuracy for peanut				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Seidenari 2003[176] EL=DS III	132 children and adults aged 3-28 years (mean 12 years) with atopic eczema (33% mild, 52% moderate, 14% severe). It was not stated whether there was a history or suspicion of food allergy. None had been treated with systemic corticosteroids, antihistamines with long half-lives (not specified) or ciclosporin for 4 months prior to the study	9%	8%	50% (all eczema)	42% (all included eczema)	33 (all ages)	90 (all ages)	25 (all ages)	93 (all ages)	It is assumed that the accuracy results represent any positive reaction.
						25 (under 6 years)	98 (under 6 years)	50 (under 6 years)	94 (under 6 years)	
						25 (6-12 years)	90 (6-12 years)	25 (6-12 years)	90 (6-12 years)	
						50 (older than 12 years)	83 (older than 12 years)	20 (older than 12 years)	95 (older than 12 years)	

NR=not reported

Diagnostic accuracy of IgE compared to an open food challenge for detection of peanut allergy

No studies

Wheat

Diagnostic accuracy of an atopy patch test compared to an open food challenge for detection of wheat allergy

Study	Population tested	Prevalence				Diagnostic accuracy for wheat				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Stromberg 2002[177] EL=DS III	141 children aged 2 months-4 years (mean 16 months) with atopic eczema, referred to an allergy unit for investigation	45% cow's milk, 55% egg, 43% wheat, 43% rye	13% milk, 14% egg, 3% wheat, 3% rye	87% cow's milk, 86% egg, 97% wheat, 97% rye	NR	90	94	92	93	93, 90, 88, and 95 respectively for rye
Jarvinen 2003[178] EL=DS III	90 children aged 2.5-36 months with atopic eczema and cow's milk allergy – they had shown a good response to cow's milk elimination but had residual symptoms (atopic eczema or gastrointestinal symptoms), and were therefore suspected of, and tested for, cereal allergy	73%	12% (73% wheat, 9% each rye, barley, oats)	61% (40% wheat, 9% rye, 7% barley, 44% oats) (67% of these reactions were eczema)	NR	67 (76 in children aged less than 1 year, 68 for age 1-2 years, 33 for age 2-3 years)	79 (71 in children aged less than 1 year, 83 for age 1-2 years, 100 for age 2-3 years)	90	46	Antihistamines were discontinued 72 hours – 6 weeks before patch testing. TCS were not allowed. Eczema was stable /controlled when testing was undertaken. Food challenge: undertaken after a 2 week diet free of cereal (child and mother). Cow's milk and cereal were given in increasing doses as inpatients for 3 days, then continued at home. Symptoms indicative of a positive reaction were anaphylaxis, urticaria, atopic eczema, vomiting, diarrhoea. Immediate reactions – those occurring within 1 hour. The results reported represent the results of the fist cereal challenge only (the challenge continued weekly at home). Atopy patch test: undertaken during the elimination diet. Skimmed milk powder and cereal (flour) applied to the back using a 12mm finn chamber, and left under occlusion for 48 hours. Results were read at 72 hours, and oedema and eczema were taken as positive reactions. Skin prick tests on the volar forearm using commercial cow's milk extract and cereals. Reactions were read at 15 minutes; test positive if the diameter of the wheal was 3mm or more and at least half the size of the positive control. Histamine was used as a positive control, and sodium chloride as a negative control.

Study	Population tested	Prevalence				Diagnostic accuracy for wheat				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Both immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
										It is assumed that the accuracy results represent any positive reaction. Results quoted for cereal (wheat) challenge.

NR=not reported

Diagnostic accuracy of a skin prick test compared to an open food challenge for detection of wheat allergy

Study	Population tested	Prevalence				Diagnostic accuracy for wheat				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Stromberg 2002[177] EL=DS III	141 children aged 2 months-4 years (mean 16 months) with atopic eczema, referred to an allergy unit for investigation	45% cow's milk, 55% egg, 43% wheat, 43% rye	13% milk, 14% egg, 3% wheat, 3% rye	87% cow's milk, 86% egg, 97% wheat, 97% rye	NR	13	98	80	60	15, 99, 90, and 60 respectively for rye
Jarvinen 2003[178] EL=DS III	90 children aged 2.5-36 months with atopic eczema and cow's milk allergy – they had shown a good response to cow's milk elimination but had residual symptoms (atopic eczema or gastrointestinal symptoms), and were therefore suspected of, and tested for, cereal allergy	73%	12% (73% wheat, 9% each rye, barley, oats)	61% (40% wheat, 9% rye, 7% barley, 44% oats) (67% of these reactions were eczema)	NR	23	100	100	32	Results quoted for cereal (wheat) challenge
Varjonen 1995[180] EL=DS III	34 children aged 'under 1 year' to 11 years with severe and extensive atopic eczema suspected of food allergy. (24 underwent food challenge)	63%	33%	66%	NR	86	100	100	82	All were treated with topical hydrocortisone (strength not stated). Eczema was 'at most mild' when testing was done. An exclusion diet (excluding the suspected foods) was used for at least 2 weeks before testing. Foods: cereals given in doses of 1, 5, and 10g. Challenge stopped if symptoms appeared. Immediate - occurring within 2 hours. What constituted a positive delayed reaction was not stated. Skin prick test: purified gliadin in ethanol applied to the volar surface of the arm, development of wheal of 3mm diameter and more than half that of the positive control (histamine) was regarded positive. IgE (CAP RAST) to wheat, rye, barley, oats and

Study	Population tested	Prevalence				Diagnostic accuracy for wheat				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
										gluten. A level of more than 0.5ku/l was reported to be considered positive. However in the diagnostic accuracy tale a level of more than 5.5ku/l was quoted. It is assumed that diagnostic accuracy relates to any reaction.

NR=not reported

Diagnostic accuracy of IgE compared to an open food challenge for detection of wheat allergy

Study	Population tested	Prevalence				Diagnostic accuracy for wheat				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Varjonen 1995[180] EL=DS III	34 children aged 'under 1 year' to 11 years with severe and extensive atopic eczema suspected of food allergy. (24 underwent food challenge)	63%	33%	66%	NR	93	56	78	83	IgE (CAP RAST) to wheat, rye, barley, oats and gluten. A level of more than 0.5ku/l was reported to be considered positive. However in the diagnostic accuracy tale a level of more than 5.5ku/l was quoted. It is assumed that diagnostic accuracy relates to any reaction.

NR=not reported

Studies for which a range of allergens were tested but accuracy data not reported for each allergen separately

Study	Population tested	Prevalence				Diagnostic accuracy for various food allergens				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
de Waard-van der Spek 1998[173] EL=DS III	64 children aged under 4 years with atopic eczema and suspected food allergy	36%	NR	NR	NR	83	100	100	91	Diagnostic accuracy of SAFT vs open food challenge – it is unclear whether this was for immediate or delayed reactions. Skin prick tests and IgE levels were also measured, and the level of agreement between the proportion of positive results noted. However it was not possible to calculate diagnostic accuracy of these tests from the data given. Food challenge: No details of the foods, other than they were cow's milk, egg and peanuts. Increasing doses were given. Positive reactions – urticarial rash, flare-up of eczema, itching, increased pulse rate, (other also listed). The test was stopped if a positive reaction was observed. If no reaction occurred, the child left hospital. Parents were encouraged to contact a dermatologist if a late (not defined) reaction occurred.

NR=not reported

Combined data

Study	Allergen (any type of reaction)	Tests	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cudowska 2005[171]	Cow's milk	Atopy patch test + skin prick test + specific IgE (for immediate and delayed reactions combined)	92 (under 3 years) 80 (over 3 years)	71 (under 3 years) 89 (over 3 years)	85 (under 3 years) 80 (over 3 years)	17 (under 3 years) 11 (over 3 years)

EL=DS III

Studies investigating different ways of undertaking the same test

Study	Population tested	Prevalence				Diagnostic accuracy for various food allergens				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
Niggemann 2002[182] EL=DS III	30 children aged 3-58 months with atopic eczema and suspected food-related symptoms.	48% milk, 20% egg, 64% sow, 22% wheat 0 placebo	NR	NR	NR	Milk 60 (12mm) 0 (6mm)	Milk 100 (12mm) 100 (6mm)	Milk 100 (12mm) 0 (6mm)	Milk 73 (12mm) 52 (6mm)	Antihistamines were stopped for at least 72 hours before testing. TCS were allowed. Food challenge: 55 challenges undertaken. Placebo: neocate. Test: fresh pasteurised milk, raw egg, wheat powder, soya milk. Provocation stopped if clinical symptoms were observed or when the highest dose was reached. Children were observed as inpatients for 48 hours after each challenge. Positive test: if one or more of the following: urticaria, angioedema, wheezing, vomiting, diarrhoea, abdominal pain, shock, or exacerbation of eczema. Patch test: using Finn chambers of 6mm or 12mm in diameter. Foods (as in the DBPCFC): 50microlitre or 20microlitre respectively used. Sites checked after 20 minutes for immediate reactions. Site occluded for 48 hours, read after 20 minutes, and again at 72 hours. Skin prick testing was also undertaken.
						Egg 71 (12mm) 29 (6mm)	Egg 100 (12mm) 100 (6mm)	Egg 100 (12mm) 100 (6mm)	Egg 67 (12mm) 44 (6mm)	
						Soya 100 (12mm) 0 (6mm)	Soya 100 (12mm) 100 (6mm)	Soya 100 (12mm) 0 (6mm)	Soya 100 (12mm) 82 (6mm)	
						Wheat 100 (12mm) 0 (6mm)	Wheat 89 (12mm) 100 (6mm)	Wheat 75 (12mm) 0 (6mm)	Wheat 100 (12mm) 75 (6mm)	
Heine 2006[185] EL=DS Ib	87 children aged 0.5-13.5 years (mean 2.4 years) with atopic eczema and suspected food allergy to cow's milk, hen's egg, wheat and soya.	45%	75%	11%	15%	Mild erythema (39%): 45	67	53	59	Topical and systemic corticosteroids were discontinued 72 hours before testing. DBPCFC 'as per previously published protocol' 165 were undertaken. Atopy patch test: one drop fresh pasteurised cow's milk, fresh soya milk, whisked whole hen's egg and a wheat gluten flour suspension applied to the skin and covered with 12mm Finn chambers for 48 hours. Skin changes graded as none, mild, moderate, severe, induration, papule formation, vesiculation, and presence of
						Moderate erythema (10%): 15	93	65	57	
						Any severity (49%): 60	60	56	64	
						Minor induration (11%): 15	92	61	56	
						Extensive (5%): 9	99	88	57	
						Any severity	91	69	59	

Study	Population tested	Prevalence				Diagnostic accuracy for various food allergens				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
						(16%): 24				a crescendo phenomenon (increase in severity of reaction between hours 48 and 72).
						Papules (1-3, 16%): 19	87	54	56	
						4-6 (12%): 12	89	47	55	Personnel reading the patch test results were blind to the results of the DBPCFC.
						7 or more (12%): 21	96	80	59	
						any papules (39%): 60	74	60	74	Diagnostic accuracy results are for delayed reactions.
						Crescendo (8%): 11	93	57	56	
						Moderate erythema + crescendo (3%): 5	99	80	56	
						Induration + crescendo (3%): 4	98	60	55	
						Papules + crescendo (≥7; 4%) 5	98	67	55	
						Moderate erythema + induration (4%): 8	100	100	57	
						Moderate erythema + papules (≥7; 4%): 8	99	86	56	
						Induration + papules (≥7; 7%):15	100	100	58	
						Moderate erythema + induration + papules (≥7; 4%): 8	100	100	57	
						Moderate erythema or induration (27%): 41	86	70	64	

Study	Population tested	Prevalence				Diagnostic accuracy for various food allergens				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
						Moderate erythema or papules (≥7; 18%): 27	90	69	60	
						Induration or papules (≥7; 21%): 31	87	66	60	
						Moderate erythema or induration or papules (≥7, 26%): 36	82	63	61	
Verstege 2005[184] EL=DS III	385 children aged 3 months to 14.5 years with suspected food-dependent symptoms to cow's milk, egg, wheat, and/or soya. 87% had atopic eczema. 11% also had asthma, 6% recurrent wheezing, and 27% hay fever.	43% (63% egg, 49% milk, 28% wheat, 19% soya) 4% placebo	67%	14%	19%	Hen's egg 93% Cow's milk 85 Wheat 65 Soya 21	59 75 77 88	80 76 52 29	83 83 85 83	Antihistamines were discontinued 72 hours before testing. TCS were allowed twice daily. Food challenges 735 were undertaken. 75% were DB and 25% were open. Placebo – 280 challenges (neocate). Test: cow's milk, egg, gluten, or soya milk. Doses were titrated. Challenges were positive if objective cutaneous symptoms (urticaria, worsening of eczema), or respiratory or gastrointestinal symptoms were seen. Skin prick test: one drop of each fresh food applied to the forearm: cow's milk, native hen's egg (whisked white and yolk), gluten powder, and soya milk. Positive (histamine) and negative (saline) controls were also applied. Reactions were read at 15 minutes. A wheal size of 3mm or greater than the positive control was considered a positive reaction. Other analysis of data was undertaken: wheal diameter 13mm for hen's egg and 12.5mm for milk, would give a 95% PPV. respectively). Predictive values could not be calculated for wheat and soya.
Fiocchi 2002[190] EL=DS III	34 children aged 1-4.4 years, median 2.26 years) with atopic eczema and IgE sensitisation for	59%	NR	NR	NR	Using commercial beef extract:: 90 Using fresh	100 78.57	NR	NR	DBPCFC: with beef. No further details in this publication. Skin prick test: using extract of lyophilised skeletal muscle tissue and with raw unfrozen skeletal muscle. Positive

Study	Population tested	Prevalence				Diagnostic accuracy for various food allergens				Comments
		Positive test on challenge	Immediate reaction	Delayed reaction	Combined immediate & delayed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
	foods. They were enrolled in this study if they reported immediate symptoms attributed to consumption of beef.					beef extract:: 100				(histamine) and negative (saline) controls were also applied. Reactions were read after and unspecified time. A wheal size of 3mm or greater than the positive control was considered a positive reaction. It is not stated whether the food challenge was undertaken without knowing the results of the prick test.
Kim 2002[189] EL= DS III	292 children and older people (mean age 12 years) with atopic eczema	35% for crude milk 37% crude egg 35% crude soyabean	NR	NR	NR	Milk				Elimination diet was used for 2 weeks prior to testing.
						44 crude	86	40	75	DBPCFC: Placebo – the vehicle for DBPCFC (mixed cereal flour).
						34 commercial	70	27	72	For the food challenge skimmed milk powder, freeze-dried flour of egg and soybean powder were used.
						Egg				Determinants of a positive test were the appearance of dryness/scaling, erythema, wheal, excoriation, or papulation. An increase of 20% compared to pre-test score was also regarded as a positive reaction.
						64 crude	81	59	63	
						56 commercial	53	40	71	
						Soya				Skin prick testing: crude extracts of milk, egg, and soybean were prepared using phosphate buffered saline. Egg and soyabean were boiled for 1 hour prior to extraction. Extracts were centrifuged and supernatants collected, which were then dried. Stock solutions were than prepared. Glycerol was used as a negative control.
						54 crude	65	43	78	
						33 commercial	71	26	38	Prick testing was done on the left forearm using crude and commercial extracts. Histamine was the positive control. Reactions were read after 15 minutes. The minimum size of positive reaction was 3mm.

NR=not reported

Bibliographic information	Study type and evidence level	Aim of study	Number of patients	Patient characteristics	Outcomes and results	Comments
Darsow U;Vieluf D;Ring J; 1995 Mar 183	Study Type: Case series Evidence Level: 3	To compare the proportion of positive results to an atopy patch test when two different concentrations and vehicles were used.	Total No. of Patients = 36 Children and adults with atopic eczema N = 36	Children and adults, aged 3-69 years (mean 29 years) with atopic eczema. Of these 16 reported eczematous reactions after exposure to at least one of the three allergens tested (HDM, cat dander, grass pollen). All were in the stable phase (partial or complete remission).		Source of Funding: None declared. Comments: Antihistamines and systemic/topical corticosteroids were discontinued for 7 days before testing. The patch testing use two concentrations, 1000 protein nitrogen units (PNU)/gm, and 10,000 PNU/gm, in two different vehicles (white petrolatum/10% isopropyl myristate and methylcellulose hydrigel/10% propylene glycol). Lyophilised grass pollen extracts were used. The patch was applied for 72 hours under 12mm Finn chambers. They were evaluated at 48 & 72 hours and classified as follows: (+) erythema, + erythema, infiltration, none or few papules, ++ erythema, intensive filtration, many papules, occasionally vesicles, and +++ for densely aggregated papules and vehicles. Skin prick tests were also done (no details, no definition of a positive test), and IgE (total and specific) levels measured. 'Concordance' between the tests was also reported (not defined) - data not reproduced here.
Perackis K;Staden U;Mehl A;Niggemann B; 2004 188	Study Type: Case series Evidence Level: 3	To compare the results of a skin prick test using whole egg and egg white.	Total No. of Patients = 45 Children who underwent skin prick testing N = 45	Children aged 6-113 months with suspected allergy to hen's egg. 96% had atopic eczema.		Source of Funding: None declared. Comments: Two drops of egg were applied to the volar forearm (one drop of whisked native whole egg, one drop of native egg white). Reactions were read after 15 minutes. A positive test was indicated by a wheal diameter of 3mm or more, without reaction of the negative control (sodium chloride 0.9%). All responded to histamine dihydrochloride (the positive control). Antihistamines and corticosteroids were prohibited 48 hours before testing.

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Niggemann B;Binder C;Dupont C;Hadji S;Arvola T;Isolauri E; 2001 Apr 200	Study Type: Randomised Controlled Trial Evidence Level: 1+	Total number of patients = 73 Amino-acid based formula N = 42 Extensively hydrolysed whey formula N = 31	Infants aged 1-9 months (median 5.7 months) with atopic eczema and proven cow's milk allergy/intolerance (on DBPCFC). Mean SCORAD scores 24.6 (0-72). Median total IgE 16.0 kU/L (less than 2.0 yo 4710.0).	Amino-acid formula vs Extensively hydrolysed whey formula	Outcomes at 6 Months: SCORAD No numerical data for each group (data shown in graphs only). Mean overall score at endpoint: 10.7 (95% CI 71 to 14.2, p<0.0001) vs Growth No numerical data (shown only in graphs). Reported that there was a statistically significant increase in length standard deviation scores in the amino-acid group, p<0.04; weight-for-length scores developments were 'similar' in both groups.	Source of Funding: SHS, Liverpool UK. The amino-acid based formula used was Neocate, and the whey formula Alfare or Pepti-Tutteli. Quantities consumed were not specified. Energy intake was similar in both groups.
Businco L;Benincori N;Nini G;Businco E;Cantani A;De Angelis M; 1986 Dec 219	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 31 Sodium cromoglicate + exclusion diet N = 31 Placebo solution + exclusion diet N = 31	Children aged 6 months-10 years with severe atopic eczema requiring 'continuous treatment' (not defined) but not corticosteroid therapy (not stated whether topical or systemic). The children also had evidence of exacerbation of symptoms caused by eating one or two foods (established by challenge tests at home). They had positive skin tests to 'a range of allergens' and serum IgE levels higher than the normal range for their age. 39% also had asthma, 26% allergic rhinitis, 10% conjunctivitis, and 6% urticaria.	Sodium cromoglicate + exclusion diet vs Placebo + exclusion diet	Outcomes at 8 Weeks: Severity* No numerical data; results shown in graphs only. p=NS between treatments when the cross-over sequence was sodium cromoglicate followed by placebo. p<0.05 in favour of sodium cromoglicate when placebo was taken first in the crossover sequence. vs Parent rating of symptoms No numerical data; results shown in graphs only. p=NS between treatments when the cross-over sequence was sodium cromoglicate followed by placebo. p<0.01 in favour of sodium cromoglicate when placebo was taken first in the crossover sequence. vs Opinion as to which treatment 'most	Source of Funding: Fisons Ltd supplied drugs The study was a DB crossover trial with 2x8-week treatment periods with a 2-week washout period in between. [EL=1-] because no baseline data and analysis was undertaken on fewer children than were randomised. Withdrawals: 8, due to lack of response (2 - excluded from the analysis); non-adherence (2); and ineffective treatment (4). Exclusion diet: based on skin test and IgE results. Cow's milk and egg was eliminated in 81%, fish in 6%, and wheat in 13%. The diet was taken for weeks 1-4 of the 8-week treatment period, and then foods reintroduced stepwise. Severity assessed by dividing the body into ten areas which were assessed for redness/weeping/vesiculation/crusting, excoriations, lichenification on a scale of 0-3,

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					effective' Sodium cromoglicate: 52% parents rating, 68% clinician's rating Placebo: 13% and 6% respectively Both: 16% and 0% respectively Neither: 3% and 10% respectively. vs Adverse effects 6% transient worsening at the beginning of the trial 0% dizziness 0% drowsiness 3% bowel disturbance vs 3% transient worsening at the beginning of the trial 3% dizziness 3% drowsiness 6% bowel disturbance	none-severe. Maximum total score 240. Parents recorded daytime itch, sleep disturbance due to itch, weeping, and redness on a 0-3 scale (maximum score 12). Dose of sodium cromoglicate: 400mg daily for children of 10-20kg bodyweight, 800mg daily for 20-30kg, 1200mg for 30-40kg, 1600mg for >40kg. The daily dose was taken in four divided doses. No topical or systemic corticosteroids were allowed.
Businco L;Meglio P;Amato G;Balsamo V;Cainelli T;Cantone P;Castro M;Coletta A;Corrias A;Giorgi PL;Grazioli I;Longo-Papadia L;Marcucci F;Masi M;Pavesio D;Scotta S;Seidenari S;Vierucci A; 1996 Mar 216	Study Type: Randomised Controlled Trial Evidence Level: 3	Total number of patients = 1085 Restricted diet* N = 505 Oral sodium cromoglicate N = 506	Children aged 5 months - 14 years (median 2 years) with AE. 58% also had a personal history of atopy, e.g. asthma, rhinitis.	Restricted diet* vs Oral sodium cromoglicate	Outcomes at 4 Weeks: Severity Change in proportion with severe AE: from 43%-13% vs 48%-15% Change in proportion with mild AE: from 23%-69% vs 19%-61%, p<0.001 from baseline for both groups for both outcomes, 'no significant differences' between groups (no p value stated) vs Extent Change in % whose extent severe: 35%-17% vs 36%-21% Change in % whose extent mild: 29-51% vs 27-44% vs Adverse effects	Source of Funding: none declared EL=1- because only 80% analysed (overall 93% completed, 82% in the diet group and 91% in the sodium cromoglicate group). *Restricted diet consisted of rice, lamb, turkey, lettuce, cooked carrots, sweet potatoes, pears, olive oil, mineral water, black tea, salt, brown sugar. Sodium cromoglicate: 80mg/kg/day in four divided doses - powder diluted in 20ml water. Mean dose used was 71mg/kg. Children were randomised to treatment irrespective of SPT and RAST results. Severity: pruritus, erythema, vesiculation, papules, excoriation, scale crusting and lichenification assessed on a 4-point scale (1-4, no symptoms - severe). Total score = score for

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
						each area x 20. Global score: 140=absent, 141-170 mild, 171-200 moderate, more than 200 severe.
					1% diarrhoea 0.5% lack of appetite 0.2% restlessness 0.2% weight loss vs	Extent: according to the number of body areas involved; o=absent, 1-5 mild, 6-10 moderate, more than 10 severe.
					Adverse effects	Treatment considered effective when at least 40% improvement of the global score occurred.
					1% diarrhoea 1% vomiting 1% nausea 0.2% lack of appetite 0.2% restlessness 2% abdominal pain 0.4% headache 0.4% pruritus 0.2% rash 0.2% urticaria 0.2% constipation 0.2% joint pain	Significantly more children in the diet group had positive tests to foods on SPT. Results were compared for children with positive or negative tests - 'no significant differences' in response were noted (data presented in graphs only).
Ewing CI;Gibbs ACC;Ashcroft C;David TJ; 1991 [220]	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 50 Zinc sulphate (sustained release capsules containing 61.8mg zinc sulphate) N = 25 Placebo N = 25	Zinc vs Placebo	Children aged 1-16 years (mean 8 years) with atopic eczema, being treated with emollients and TCS, and some with trimeprazine.	Outcomes at 8 Weeks: Itch 4.6 vs 3.4, p=0.01 vs Sleep disturbance No numerical data, p=0.77 between groups vs Trimeprazine dose No numerical data, p=0.11 between groups vs	Source of Funding: Smith Kline French supplied drugs [EL=1-] as only those who completed treatment were analysed. Withdrawal rates were 6% zinc and 10% placebo; reasons were nonadherence (1 each group), diarrhoea (1 placebo), 1 exacerbation of eczema (1 zinc), itchy rash (1 zinc, 2 placebo), Herpes simplex infection (1 placebo). Usual treatment continued during the study. Families recorded redness, daytime itch, and night-time sleep disturbance on a 1-10 scale. Severity: body divided into 14 areas and the surface area affected estimated. Each area score on a scale of 1-5 for severity. Surface area x severity = combined disease severity score.

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					TCS quantity applied 259.3g (mean) vs 188g (mean), p=0.23 vs Emollient quantity applied 1159.1g (mean) vs 511.6g (mean), p=0.13 vs Surface area score (mean change) +5.5 (29%) vs +1.6 (11%), p=0.53 vs Erythema score (mean change) -0.1 (4%) vs -0.4 (17%), p=0.10 vs Combined disease severity score (mean change) -12.6 (35%) vs -4.7 (14%), p=0.60	
Graham P;Hall-Smith SP;Harris JM;Price ML; 1984	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 29 Sodium cromoglicate N = 29	Children aged 3-12 years (mean 7 years 5 months) with chronic AE requiring regular attendance at outpatient clinics. Children were treated with a 'tailored diet' which was not detailed, other than foods were eliminated and re-introduced according to IgE levels.	Sodium cromoglicate vs Placebo	Outcomes at 27 Weeks: Severity (mean score change) -0.69, p<0.01 vs baseline vs	Source of Funding: Fisons Ltd provided study medication DB cross-over RCT. Only 76% completed and were analysed [EL=1-]. Sodium cromoglicate dose: 100mg four times a

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
[217]		Placebo N = 27	Baseline severity score 2.09, extent 1.98.		-0.63, p<0.01 vs baseline vs Extent (area; mean score change) -0.10 vs -0.16	day before meals (capsules) for 3 weeks increasing to 200mg for next 3 weeks. Treatment periods were of 6 weeks' duration, with a 2-week washout in between (usual diet). Symptoms, severity and extent were measured on a 4-point scale. All previous medication for AE was stopped and all were given HC 1% (not stated whether cream or ointment), and emulsifying ointment as needed.
Leung TF;Ma KC;Cheung LT;Lam CW;Wong E;Wan H;Hon EK; 2004 Dec [212]	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 15 Amino-acid based elemental diet* N = 15 Control N = 15	Infants and young children aged under 3 years (median 1.4 years, IQR 0.6-2.6) with AE. All had a positive SPT to at least one of six food allergens (cow's milk, soy, whole egg, peanut, wheat, mixed fish), and raised cow's milk or soya bean specific IgE (35 KaU/L or more). Median SCORAD 23.9 (IQR 10.5-29.7).	Amino-acid-based elemental diet vs Control	Outcomes at 5 Months: SCORAD treatment different 3.97, p=0.274 treatment x period interaction 7.23, p=0.012 vs Parental global health score (VAS 1-9, worst-best) treatment difference 0, p=0.792 treatment x period interaction 0.01, p=0.958	Source of Funding: Chinese University of Hong Kong EL=1- because no baseline data reported therefore not known whether groups were similar at baseline. Only completers were analysed (73%). The reasons for the 4 withdrawals were: 2 drank less than required, 1 refused to drink the amino-acid formula, 1 had 'too mild' AE. The amino-acid formula used was Neocate. 500ml or more was advised to be taken (not stated whether this is per day). No dairy or soya based products were allowed during the study. The control group continued with their pre-existing formula. A dietician conducted a nutritional assessment. All treatments for AE remained unchanged (TCS and sedating antihistamines). Severity was assessed by a paediatric dermatologist unaware of treatment allocation. The positive tests to skin prick allergens were: cow's milk, soya bean, wheat, mixed fish (all 1 each), whole egg (11), mixed peanuts (4),

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
						house dust mite (6). Daily fluid and energy intake did not differ before and after the interventions. Treatment was given for 6 weeks with a 6 week washout in between.
Tsoureli-Nikita E;Hercogova J;Lotti T;Menchini G; 2002 Mar 221	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 96 Vitamin E (400 units [268mg]) once daily N = 50 Placebo N = 46	Children and adults aged 10-60 years with moderate-severe atopic eczema affecting 30-70% of body surface area.	Vitamin E vs Placebo	Outcomes at 8 Months: Global assessment (response to questionnaire) 8% worsened 12% no change 20% slight improvement 46% great improvement 14% almost complete remission vs 78% worsened 11% no change 9% slight improvement 2% great improvement 0% almost complete remission vs Adverse effects none vs none	Source of Funding: None declared [EL=1-] because although the study is described as randomised in the abstract the methods would suggest that the treatments were not allocated randomly. No baseline data were reported. Only petrolatum emollients were permitted during the study.
Viljanen M;Savilahti E;Haahtela T;Juntunen-Backman K;Korpela R;Poussa T;Tuure T;Kuitunen M;		Lactobacillus (5x10 -9 colony forming units) N = 80 Mixture of probiotics (Lactobacillus, Bifidobacterium, Propionibacterium)		Lactobacillus vs Mixture of probiotics (Lactobacillus, Bifidobacterium, Propionibacterium) vs Placebo	Outcomes at 1 Months: SCORAD (all infants - mean score change) -16.6 (48%) vs -14.0 (42%) vs	DB RCT. Only 91% completed and analysed; reasons for withdrawals were: moved away (2), did not start diet because symptoms alleviated (11), unable to tolerate diet (4), protocol too difficult (3). Eczema lesions were treated with emollients and HC 1% (not stated whether cream or ointment).

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
2005 Apr		N = 76			-14.2 (47%), p=NS between groups	The probiotics and placebo were given as capsules mixed with food, twice daily.
[222]		Placebo N = 74			SCORAD (in 52% with verified cow's milk challenge - mean score change) -15.1 (45%) vs -14.5 (43%) vs -15.2 (46%), p=NS between groups	The dose of Lactobacillus given was 5x10 (-9) colony forming units.

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes	Comments
Brouwer ML; 2006 Jul 224 Country: Netherlands	Study Type: Randomised Controlled Trial Evidence Level: 1-		Total No. of Patients = 50 Hydrolysed whey formula + Lactobacillus rhamnosis N = 17 Hydrolysed whey formula + Lactobacillus N = 16 Control: hydrolysed whey formula only N = 17	Infants (age 1.1 - 5.2 months) with AE and suspected cow's milk allergy routinely attending a baby health clinic.	Outcomes at 3 months: Reduction in SCORAD index	Funding: Not stated SCORAD index was reduced in all groups irrespective of treatment implying reasons other then the studied intervention caused this reduction.
Agata H;Kondo N;Fukutomi O;Shinoda S;Orii T; 1993 Feb 205	Study Type: Cohort Study Evidence Level: 2-		Total No. of Patients = 150 Children 3 months- 13 years with sensitivity to hen's egg or cow's milk (on basis of history and food challenges) N = 43 Nonatopic healthy children without milk or egg sensitivity N = 64 Children sensitive to egg and milk with urticaria, angioedema, acute gastroenteritis within 1 hour of the food challenge N = 53	Children aged 3 months - 13 years with atopic eczema with positive food challenge to eggs/milk, or who developed urticaria, angioedema, acute gastroenteritis, and bronchial asthma within 1 hour of the challenge test, and a control group who did not have atopy.	Outcomes at 3 Months: Severity in those sensitive to egg (n=33) in 27 who had elimination diet, 23 improved by one category, 4 improved by 2 or more (at baseline 7 were mild, 13 moderate, 7 severe) in 6 who did not have an elimination diet, 4 had no improvement, 2 worsened by one category (at baseline 1 was mild, 5 moderate) Severity in those sensitive to milk (n=21) in 16 who had elimination diet, 1 was unchanged, 10 improved by one category, 5 improved by 2 or more (at baseline 1 was mild, 9 moderate, 6 severe) in 5 who did not have an elimination diet, 2 had no improvement, 3	Funding: Ministry of public welfare, Japan Only 43 of 54 'randomly selected' children were treated with elimination diets; the other 11 continued with the 'offending' foods. Severity of AE was graded on the basis of food-challenge symptom scores, where 0=absent, 1=mild, 2=moderate, 3=severe. DBPCFC was performed if there was a clear-cut history of major allergic skin symptoms after ingestion of a specific food or if there was a chance of systemic anaphylaxis. The food challenge consisted of egg, milk, or placebo.

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes	Comments
					worsened by one category (at baseline 2 were mild, 3 moderate)	
Devlin J;David TJ;Stanton RH; 1991 Jan 209	Study Type: Case series Evidence Level: 3	To describe the treatment of children with atopic eczema with a diet eliminating all but six foods.	Total No. of Patients = 43 Elemental food (100% free amino acids) N = 43	Children included in the Devlin 1991 study.[208] Those who were subsequently treated with an 'extreme antigen avoidance regimen' including an elemental diet (100% free amino acids) in hospital using Vivonex . At baseline median 70% (20-96%) body surface area was affected. Median erythema score was 3 (2-3), median severity score 210 (60-288).	Severity Median score: 33% of baseline score (3-134%) Global success/failure 27% treatment failures (score same or worse than at beginning) 73% treatment success (median reduction to 27% of baseline score [3-67%]; 96% were only using emollients at the end of treatment) Adverse effects 89% (of n=34) lost up to 17% body weight. 19% loose stools 0% electrolyte disturbance serum albumin fell in 93% (of n=27), from mean 30.8g/l to mean nadir of 21.2g/l	Source of Funding: North Western Regional Health Authority Comments: Of the 43 children, 1 declined the intervention, 2 refused to drink the formula feed, and only 37 who had been followed up for 12 months or longer were analysed. Severity score = surface area affected x degree of erythema (0-3). All mammalian and avian pets were removed from the home. Investigators 'ensured that rigorous measures' were taken to reduce house dust mite levels in the bedroom. Corticosteroids (not stated whether topical) were discontinued at the time of hospital admission, but emollient and trimeprazine (night sedation) were continued. All were also given an appetite stimulant (cyproheptadine 2mg twice daily). All usual food and drink (including water) were excluded, and the child fed exclusively on unlimited quantities of unflavoured Vivonex. A low concentration was used to start, gradually increasing to isotonicity on day 3. After 28 days if there was little or no improvement (not defined), the diet was abandoned and systemic corticosteroids or TCS used instead. If there was moderate improvement, the elemental diet was extended for 1-2 weeks. If 'largely unresolved', open food challenges were

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes	Comments
						commenced. The demographics and clinical features of treatment failures were compared with those for whom treatment was successful, and ' no significant differences' were found. Children were discharged from hospital once established on three foods, at which point Vivonex was discontinued. After the first week at home, food challenges were continued, and if positive repeated at intervals of 6-12 months. The number of food challenges done and the number of positive tests were reported - data not reproduced here.
Sloper KS;Wadsworth J;Brostoff J; 1991 Aug 196	Study Type: Case series Evidence Level: 3	To investigate whether food elimination in childhood eczema would improve the condition in at least some patients.	Total No. of Patients = 91	Children aged 0.42-15 years (median 4.5 years) with AE. Baseline severity score: median 32 (range 0-80). 76% were breast-fed; cow's milk had been given to 96%. Foods exacerbated AE in 56% - mainly egg or cow's milk (each 28.6%), followed by colourings (13.2%).	Severity (median score change) -6 (-36 to 10), p<0.001	Source of Funding: Heinz provided tinned foods for challenge test Comments: Withdrawal rate 27% (66 provided adequate pre- and post-elimination diet data). *elimination diet (started when eczema was stable): eggs, cow's milk, and 'other foods according to history'. Other foods avoided included: 42% nuts, 36% fish, 26% food colours, 23% tomatoes and wheat, 21% citrus fruit, 18% potato, 17% soya and chocolate. Dietary advice was given by a dietician. 52% were avoiding at least one food at the start of the study (32% egg, 13% cow's milk, 10% nuts). Cow's milk and egg challenges were undertaken in some - data not reproduced here.

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes	Comments
						Usual treatment was unchanged. Severity score reached by dividing body into 20 areas and each assessed for the presence or absence of erythema, vesiculation, excoriation, lichenification (maximum score 80).
Pike MG;Carter CM;Boulton P;Turner MW;Soothill JF;Atherton DJ; 1989 Dec 211	Study Type: Case series Evidence Level: 3	To investigate the effects of a few foods diet in children with atopic eczema	Total No. of Patients = 66 Few foods diet* N = 66	Children aged 0.6-16.8 years (mean 4.2 years) with severe atopic eczema inadequately controlled by standard topical treatment (no further details). 42% had at least one hospital admission for atopic eczema, 91% were woken by itching more than 50% of nights, 53% had previous dietary treatment for their eczema, 52% were already excluding one or more foods at start of the study.	'Worthwhile improvement' (not defined) 46% parental opinion 35% investigator's opinion Reintroduction of foods** 25% deteriorated months 1-3 15% withdrew despite 'benefit' (diet too burdensome) 60% persisted (mean 47.9 weeks, range 26.4-71.1)	Source of Funding: none declared Comments: Median duration of follow-up was 26 weeks (range 19-44). Some underwent skin prick testing for cow's milk, egg, dog fur, cat fur, HDM, grass pollen. *the diet was individually tailored: foods implicated in the exacerbation of eczema (generally or in the child) were excluded. The diet was as strict as the child could tolerate and palatable enough to ensure adherence. Mean number of foods taken: 8.76 (SD 3.76), range 1-19. Children who responded to the diet, with parental agreement, continued serial reintroduction of individual foods at weekly intervals. Those who successfully completed the food reintroduction underwent DBPCFC (n=10). Those who did not respond either discontinued or proceeded to a second diet, similar in type but with different constituents. **in children who the investigator thought had improved. Severity assessed on 20 body areas, each on 0-3 scale for redness, surface damage, lichenification. Parents recorded itch, redness, and

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes	Comments
						sleep disturbance (0-3). Adverse effects were not considered. % improvement - numerical data were only reported for the 'diet responsive' group. Characteristics of responders and non-responders were reported (data not reproduced here).
Aoki T;Kojima M;Adachi J;Okano M; 1992 199	Study Type: Case series Evidence Level: 3	To ascertain the relationship between the effect of egg exclusion and egg allergy.	Total No. of Patients = 213 Egg exclusion diet N = 213	Infants aged under 3 years with infantile or atopic eczema. Exclusions: purely milk-fed infants, infants already on egg exclusion diet, eating small amounts of egg, infants with severe skin symptoms, and those who needed immediate treatment.	Skin condition 'better' (not defined) 48.5% in children aged 3-6 months (n=33) 44% in children aged 7-11 months (n=25) 19.6% in children aged 1 year (n=46) 17.6% in children aged 2 years (n=34) Results according to positive vs negative test for egg allergy (n=99 only): 70% vs 30% 37.5% vs 62.5% 28.6% vs 71.4% 0 vs 100% respectively (for age groups as listed above)	Source of Funding: none declared Comments: RAST test performed for egg white, milk, soybean, wheat, house dust mite (scores of 2 or more regarded as positive). Condition of skin at follow-up was compared to sketches and photographs taken at the first visit (without knowing the results of RAST). At the first visit the skin symptoms were graded into 3 categories. Infants considered allergic if either RAST or skin test proved positive. The study was called a 'controlled' trial but there was no control group evident in the paper. Authors also explore the effects of egg exclusion in those with positive and negative RAST or SPT to egg or other allergens, and between age groups. 'Correlation' reported between egg exclusion and allergy in infants aged 3-6 months. Correlation reported between egg exclusion and a positive test to egg allergy for the age group 3-6 months

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes	Comments
						(only). Withdrawals due to: non-attendance (11%) nonadherence (17%) restricted foods other than egg (36%) change of symptoms (infections; 16%) change of treatment (12%) 'effect no indicated' (8%)
Businco L;Businco E;Cantani A;Galli E;Infussi R;Benincori N; 1982 Jul 195	Study Type: Case series Evidence Level: 3	To investigate the efficacy of milk and/or egg free diets in children with severe AE.	Total No. of Patients = 59 Cow's milk elimination (plus/minus egg elimination) N = 59	Children aged 2-14 years (mean 4 years and 2 weeks) with severe and chronic atopic eczema. They had been referred to the Allergy & Immunology section of a paediatric hospital department after no improvement from usual treatments (antihistamines, TCS and systemic corticosteroids).	Global response to treatment 80% 'cured or improved' 20% unchanged	Source of Funding: None declared Comments: *the elimination diet was tailored to the history of suspected allergy. The proportions having either or both foods eliminated was not stated. Skin tests, IgE levels were undertaken, but children were treated with an eliminiation diet regardless of these test results. Skin tests for cow's milk proteins were positive in 30, for egg in 5, and for both egg and cow's milk in 10. Response to treatment was also examined in terms of the child's age and age of onset of AE, family history of atopy, duration of breast-feeding, and total and specific IgE - data not reproduced here.
David TJ; 1992 210	Study Type: Case series			This study is included only as duplicate/related publication to refs [208] and [209] - there no additional data reported in this paper.		
van Asperen PP;Lewis M;Rogers	Study Type:	To describe the authors' experience with an	Total No. of Patients = 29	Children aged 2-12 years with persistent AE despite regular TCS	Parental global assessment	Source of Funding: none declared

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes	Comments
M;Kemp AS;Thompson S; 1983 Sep 204	Case series Evidence Level: 3	elimination diet in children with AE.	Elimination diet N = 29	treatment.	7 improved 3 unchanged 3 deteriorated Dermatologist's assessment 5 improved 7 unchanged 1 deteriorated	Comments: *consisting of 19 foods: lamb, chicken, beef, lettuce, carrots, parsley, pears, rice, plain flour, semolina, matzo crackers or Carrs water biscuits, sugar, golden syrup, honey, oils, vinegar, salt and pepper, and coffee. 55% withdrew from the diet, in 28% this was because the diet was too restrictive. The study design was as follows: 2 weeks of usual diet (baseline), 2 weeks of the elimination diet, then reintroduction of foods at the rate of a new one every 2 days (limited details reported for the latter stage). Outcomes were assessed using parental diary card, with sleep and itch scores (both using scales of 0-3 none-severe). In addition, a dermatologist assessed severity (inflammation, lichenification, and cracking, all on a grade of 1-2); a change of 2 or more was considered significant. The authors also reported that there were significant improvements in itch score and in the area of eczema affected, and no significant difference in sleep score or severity (data shown in graphs only).
Martino F;Bruno G;Aprigliano D;Agolini D;Guido F;Giardini O;Businco L; 1998 Nov	Study Type: Case series Evidence Level: 3	To investigate the effectiveness of a home-made meat-based formula and its adequacy as a diagnostic tool for children with food-induced atopic eczema.	Total No. of Patients = 16 Home-made meat-based formula (the 'Rezza-Cardi' diet) N = 16	Children aged 5-24 months (mean 9.1) with severe atopic eczema, suspected to be 'multiple food-induced'. Severity score of more than 15 (maximum score 30) and more than three positive skin prick test responses to food allergens (14 were positive to cow's milk, egg and wheat, and 2 were positive to	Severity (median score change) -21 (no p value reported) Growth No numerical data; 'all gained weight normally according to Italian	Source of Funding: None declared Comments: Severity was measured on a scale of 0-3 for 10 areas. The diet consisted of lamb meat, olive oil, pre-cooked rice flour,

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes	Comments
[214]				cow's milk, egg, and soya).	standards', and the body weight centile increased in 38% children. Lipids (mean change) Total cholesterol +1.5mg/dl (0.04 mmol/l) High density lipoprotein +8.5mg/dl (0.22 mmol/l) Low density lipoprotein -0.7mg/dl (0.02 mmol/l) Triglycerides -40.6mg/dl (0.46 mmol/l) (no change was statistically significant from baseline)	water, and sodium chloride. Calcium 300mg and vitamin D 400 units were given daily as a supplement. Fruit and age were also given according to the patient's age. Topical betametasone dipropionate was allowed for the first week of the study only. Adverse effects were not considered.
Broberg A;Engstrom I;Kalimo K;Reimers L; 1992 Sep [206]	Study Type: Case series Evidence Level: 3	To report the authors' experience of using an elimination diet to treat atopic eczema	Total No. of Patients = 13 Elimination diet* N = 13	Children aged 10 months-4 years with severe atopic eczema in spite of 'adequate' topical treatment (emollients, hydrocortisone, intermittent triamcinolone, antihistamines, and antibiotics) and elimination of the food items to which the child was suspected to be allergic.	Proportion improved 6 based on the investigator's scores 8 based on parents' scores	Source of Funding: Grants from two institutions Comments: *elimination diet: casein hydrolysate, lamb, rice, corn, corn oil, potato, cucumber, melon, bilberries, salt, sugar, and gluten and milk-free bread. The children's usual treatment for atopic eczema was continued during the study. One child withdrew due inability to keep to the diet. Not all the children who improved according to the investigator improved according to the parents, however the scoring system used was different. Investigator's rating: intensity of erythema, lichenification, vesiculation, excoriation, papules, dryness scored on scale of 0-4, none-severe, and distribution measured on scale of 0-4

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes	Comments
						(maximum total score 96). Parent's rated eczema and pruritus on a scale of 0-4, and disturbed nighttime sleep on 0-3.
Sporik R;Hill DJ;Hosking CS; 2000 187	Study Type: Case series Evidence Level: 3	To determine the minimum wheal size that rules in a diagnosis of food allergy.	Total No. of Patients = 467	Children referred for suspected food allergy. Median age 3 years.	Results: Wheal sizes of 8mm for cow's milk, 7mm for egg and 8mm for peanut are the minimums required to predict allergy on open food challenge in this high-risk population.	Source of Funding: Not stated Comments: Data are not independent as some children had more than one SPT result. Open food challenge used as reference for these wheal size data but this is not the gold standard.

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Atherton DJ;Sewell M;Soothill JF;Wells RS;Chilvers CE; 1978 Feb 25 193	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 36 Egg and cow's milk elimination diet, with soya-based milk substitute N = 36 Control: egg and cow's milk elimination diet, with a preparation containing a mixture of dried egg and cow's milk as milk substitute N = 36	Children aged 2-8 years (median 6 years) attending a dermatology clinic with 'clinically typical' atopic eczema. Of the 20 who completed the study, 3 had a previous history of exacerbation of skin symptoms after ingestion of eggs or cow's milk.	Egg and cow's milk elimination diet with soya-based milk substitute vs egg and cow's milk elimination diet, with a mixture of dried egg and cow's milk as milk substitute	Outcomes at 4 Weeks: Activity scores (treatment effect*) 2.06, p<0.001 vs Area scores (treatment effect*) 2.73, p<0.005 vs Pruritus (treatment effect*) 4.49, p=NS vs Sleeplessness (treatment effect*) 4.95, p<0.05 vs Antihistamine usage (not explained further; treatment effect*) 14.15, p<0.025 vs Activity scores (order effect*) 1.34, p<0.01 vs Area scores (order effect*) 2.02, p<0.05 vs Pruritus (order effect*) 4.74, p=NS vs Sleeplessness (order effect*)	Source of Funding: Cow & Gate provided milk powders DB cross-over RCT, withdrawal rate 44% (25% were due to 'dietary lapses', defined as drinking less than a pint of milk substitute per day or eating excluded food, i.e. non-adherence). EL=1- because only completers analysed, and lack of baseline data regarding comparability of intervention and control groups. Dietary advice given by a dietician. The elimination diet also excluded chicken and beef. Treatment/ control was given for 4 weeks followed by a 4-week 'washout' during which the usual diet was resumed. Children were asked to drink at least a pint of the milk substitute per day. Usual treatment for atopic eczema was continued (daily bath with emulsifying ointment, HC ointment 1%, oral trimeprazine). Parents recorded daytime itch and sleep disturbance on a scale of 0-3. Two dermatologists scored 20 body areas as affected or unaffected, plus 'activity' of eczema (+2 for major improvement, +1 minor improvement, 0 no change, -1 minor deterioration, -2 major deterioration). Lichenification and ichthyosis alone were ignored. *treatment effect = mean difference between groups. Order effect = difference between mean scores in the first and second treatment

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
						periods using the intervention.
					8.83, p<0.01 vs	
					Antihistamine usage (order effect*)	Prick tests were performed at the start of the second treatment period with 10 allergen solutions (including house dust mite, grass pollen, cat fur, egg, milk, control). It was also reported that there was no correlation between positive prick test to egg and cow's milk antigens and response to diet.
					3.99, p=NS	
Mabin DC;Sykes AE;David TJ; 1995 Sep [207]	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 85 Few foods diet with whey hydrosylate as milk substitute N = 27 Few foods diet with casein hydrosylate as milk substitute N = 32 Control (continued usual diet) N = 26	Children aged 0-3-13.3 years (median 2.3 years) with AE that persisted despite conventional treatment and involved 12% or more of body surface area. Exclusions: if breast-fed, had unstable or infected AE, intolerance to casein or whey hydrosylate formulas, received oral corticosteroids within 4 weeks.	Few foods diet with whey hydrosylate as milk substitute vs few foods diet with casein hydrosylate as milk substitute vs control (continued usual diet)	Outcomes at 6 Weeks: Body surface area (median change in score, 95% CI) -4.9 (-12 to -1.5), p=0.49 between groups vs -5 (-21.2 to -1.6) vs -4.9 (-12 to -1.5), p=0.49 between groups vs Skin severity score (median change in score, 95% CI) -21.8 (-30.2 to -12.8) vs -13.5 (-38 to -13.4) vs -15.9 (-22.5 to -5), p=0.88 between groups vs Sleep disturbance score (median change in score, 95% CI) -0.4 (-1.4 to 0.3) vs -0.2 (-0.7 to 0.1) vs	Source of Funding: Two authors supported by Cow and Gate Single-blind RCT. The parents and dietician who advised on the diet were blind to the identity of the milk (but not to which diet). A single observer was blind both to whether the child was receiving a diet and to which milk the child was receiving. A dietician gave advice to parents regarding the few foods diet over a 6-day period. The diet consisted of one meat, rice, potato, one of the brassicas, one fruit, and whey or casein hydrosylate formula milk. Up to three additional foods were allowed if it was judged by the dietician that compliance with the diet would otherwise be poor. Tap water and pure fruit juice (the juice of whichever fruit chosen as a food) were also permitted. Severity was measured on a scale of 0-3 for each of 32 areas (extent of area affected and degree of erythema). Sleep and itch were also assessed on a 0-3 scale. Criteria for withdrawal from the study were defined a priori (withdrawal rates were 46% overall, 67% of the whey arm, 53% of the

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					-0.1 (-0.2 to 0.2) vs Daytime itch score (median change in score, 95% CI) -0.1 (-1.72 to 0) vs Daytime itch score (median change in score, 95% CI) -0.6 (-1 to -0.21) vs 0 (-0.4 to 0.14), p=0.08 between groups	casein arm, and 15% of the control arm. 37% and 25% in the whey and casein arms respectively withdrew due to failure to adhere to the diet, compared to none for this reason in the control arm). EL=1- because only those who completed the 6- eek treatment period were analysed. 15% in the whey group, 28% in the casein group and 42% of the control group used antihistamines.
Tan BB;Weald D;Strickland I;Friedmann PS; 1996 Jan 6 [227]	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 60 House dust mite avoidance N = 30 Placebo N = 30	Children and adults aged 7-65 years with AE (defined as atopic on the basis of a positive 15 minute response to a prick-test challenge with a range of aeroallergens). 30 (50%) were aged under 17 years. Exclusions: pets, house dust mite avoidance measures, or systemic treatment for AE in the previous 6 weeks.	House dust mite reduction vs placebo	Outcomes at 6 Months: Body surface area (mean difference between groups) 10% (3-17), p=0.006 (8.3, 95% CI 2.5 to 19.1, p=0.13 accounting for mattress dust weight and carpet Der p1 concentrations) vs SASSAD (mean score change) -12.6 vs -4.2 (no baseline data) vs SASSAD (mean difference in score change) 4.2 (95% CI 1.7 to 6.7, p=0.008), accounting for differences in initial eczema scores, mattress dust weight, and bedroom carpet	Source of Funding: not declared House dust mite reduction consisted of a Goretex bedding system, benzyltannate complex spray for carpets, and a high-filtration vacuum cleaner. The placebo group used light cotton bedcovers, water with a trace of alcohol to spray on carpets and a standard upright vaccum cleaner with a poor filtration performance. A trained nurse applied the bedcovers and spray in all households. In both groups, treated carpets were vacuumed daily and the rest of the house 2-3 times per week. Soft toys were excluded from bedrooms. Use of usual range of treatments was permitted. A physician unaware of treatment group allocation examined all patients monthly.

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					concentrations vs Reduction in geometric mean dust load in mattress -98% vs -16%, p=0.002 vs Median reductions in Der P1 (antigen) concentrations in bedroom carpet -91% vs -89%, p=0.94 vs Median reductions in Der P1 (antigen) concentrations in living room carpet -76% vs -38%, p=0.27 vs Mean difference in final severity scores 4.3 (95% CI 1.3 to 7.3, p=0.006, accounting for differences in initial eczema scores, mattress dust weight, and bedroom carpet concentrations (11.1, 95% CI -3.1 to 25.3, p=0.019 in children aged under 17 years)	Dust sampling was not done after 3 months for any beds used by the intervention group because the reduction in dust seen earlier in the trial meant there was insufficient dust to sample. Withdrawal rates were 3% in the intervention group and 17% in the placebo group - of the total of 12 who withdrew, 10 were due to moving house or acquiring pets or changing carpets; 2 were due to breaking the protocol. [EL=1-] because only those who completed treatment were analysed. Analysis of variance to investigate what the treatment effect could be due to was also undertaken - data not reproduced here.
Ricci G;Patrizi A;Specchia F;Menna L;Bottau P;D'Angelo V;Masi M;	Study Type: Randomised Controlled Trial	Total number of patients = 41 House dust mite	Children aged 2-10 years (mean 3.9 years) with AE associated with high total and/or specific IgE serum levels (specific to foods or inhalant	House dust mite avoidance vs Control	Outcomes at 2 Months: SCORAD (mean score change)	Source of Funding: National Research Council, Italy [EL=1-] because no baseline data

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
	Evidence Level: 1-	avoidance	allergens).			therefore unclear whether groups similar at baseline.
2000 Aug		N = 21	Baseline SCORAD scores 33 in the intervention group and 27 in the control group.		-76%, p=0.025 vs baseline vs	
226		Control			-11%, p value vs baseline not stated. No between-group analysis. vs	House dust mite avoidance consisted of: encasing mattresses and pillows with mite microfine fibres or Goretex bedding system, a hot weekly wash of bedding, living room and bedroom vacuumed at least twice a week, soft toys washed once a week or excluded from bedrooms, carpets removed or vacuumed once a week or more. No pets allowed. Advice on mite avoidance was given by a person not involved in the later assessment.
		N = 20			Change in geometric mean dust load in beds (mg/m2)	
					-54%, p=0.014 vs baseline vs	
					-43%, p=NS vs baseline. No between-group analysis. vs	
					Change in geometric mean concentration of Der p1 and Der f1 in beds (ng/m2)	The control group continued with previous house cleaning strategies (no specific mite avoidance measures were used).
					-76%, p=0.025 vs baseline vs	No dietary restriction was used during the study.
					-58%, p=NS vs baseline. No between-group analysis.	
Cant AJ;Bailes JA;Marsden RA;Hewitt D;	Study Type: Randomised Controlled Trial	Total number of patients = 19	Exclusively breast-fed infants aged 6 months - 6 years with atopic eczema. All underwent skin prick testing for eggs, cow's milk, chocolate, cod, mixed nuts, and wheat; 8 (42%) tested positive at entry to trial 1 (see comments), and 9 (50%) at entry to trial 2.	Exclusion diet plus soya milk substitute vs	Outcomes of trial 2	Source of Funding: Wyeth supplied milk substitutes
				Exclusion diet plus cow's milk and egg milk substitute	Activity scores at weeks 2, 4, 6: 17.2, 13.2, 14.1 (p<0.001 for difference between weeks 2 and 4).	
1986 Jul 26	Evidence Level: 1-	Exclusion diet* plus soya as milk substitute N = 19				Trial 1 (DB RCT):
202			Mean activity score 17.3 (SD 9.7), and mean area score 12.4 (SD 5.8).		Area scores at weeks 2, 4, 6: 13.2, 10.7, 10.7 (p<0.01 for difference between weeks 2 and 4) vs	*excluding cow's milk, egg, chocolate, wheat, nuts. fish, beef, chicken, citrus fruits, colourings, preservatives.
		Exclusion diet* plus milk substitute containing cow's milk and egg N = 19	Exclusions: seborrhoeic dermatitis.		Outcomes at 12 Weeks:	Design: 3x4-week periods; the first two consisting of cross-over randomised treatment with the milk substitutes, the last period consisting of usual diet.
					Area score	The milk substitutes were supplied as powders for reconstitution with water; the equivalent of a pint a day was consumed. Diets were supervised by a dietician.
					9.1 on usual diet, p<0.01 vs baseline vs	

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Activity score 11.8 on usual diet, p<0.01 vs baseline vs Outcomes at 4 Weeks: Area score 9.0 vs 8.9 vs Activity score 10.4 vs 12.6 vs Outcomes at 8 Weeks: Activity score 11.2 vs 11.8 (SE for difference between means at week 8: 1.62, p=NS) vs Area score 8.3 vs 9.9 (SE for difference between means at week 8: 0.98, p=NS)	Area score: presence or absence of eczema on 20 body areas. Activity: severity on scale of 0-3 for each body area. Of 17 completers, 12 were exclusively breast-fed. Reasons for withdrawal: mother vomiting on soya substitute (n=1), baby developed eczema and bloody diarrhoea within 24 hours of cow's milk/egg substitute (n=1). It was also reported that the quantity of TCS used did not differ significantly between groups (no numerical data). Trial 2: Design: open trial for 6 weeks; 2 weeks usual diet (containing cow's milk and egg), 2 weeks exclusion diet (as in trial 1), 2 weeks usual diet. If activity scores fell by more than 20% during the exclusion diet and increased by more than 20% on reintroducing the usual diet, the mothers were invited to take part in a further randomised crossover phase of 2 other milk substitutes. However only 2 infants qualified for this and only 1 underwent the trial (data not reproduced here).
Neild VS;Marsden RA;Bailes JA;Bland JM;	Study Type: Randomised Controlled Trial	Total number of patients = 53 Egg and cow's milk	Children and young people aged 1-23 years with AE requiring regular treatment with emollients, TCS, and oral antihistamines.	Egg and cow's milk exclusion, soya milk substitute vs Control: preparation containing mixture	Outcomes at 6 Weeks: Area score (treatment difference*)	Source of Funding: South West Thames Regional Health Authority DB cross-over RCT; 25% withdrew,

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
1986 Jan 194	Evidence Level: 1-	exclusion, soya milk substitute N = 53 Egg and cow's milk exclusion, dried mixed preparation used as substitute N = 53	Positive skin prick tests to egg and/or milk were seen in 26%, and to two or more inhalant allergens in 79%. Overall 59% had an IgE level of more than 100 (units not stated).	of dried egg and cow's milk as substitute	-1 (95% CI -6 to 3.4) vs Total (day & night) itch score (treatment difference*) 15 (95% CI -21 to 51) vs Total TCS consumption (treatment effect*) fluorinated TCS: 5.8 (95% CI 1 to 10) HC 1%: 6.0 (95% CI 0.1 to 12) [i.e. greater use when treated with the trial diet]	due to non-adherence. EL=1- only completers analysed. *treatment effect = mean difference between trial and control diets. Chicken and beef were also excluded from the diet as they may contain proteins common to egg and milk. Dietician gave the dietary advice. The two 6-week treatment periods were separated by a 6-week washout where the usual diet was consumed. Usual treatment for AE was continued. Parents recorded day and night itch and sleep disturbance on a 10cm scale. Two dermatologists assessed extent and activity of AE. At the start of the trial a skin prick test for house dust mite, grass pollen, cat fur, egg or cow's milk was undertaken.
Lever R;MacDonald C;Waugh P;Aitchison T; 1998 Feb 198	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 62 Egg exclusion diet N = 28 Control N = 27	Children of mean age 11-17 months (across both groups), with AE and suspected egg sensitivity, optimally controlled with conventional topical treatment and on stable maintenance treatment using mild-moderate TCS at the time of entry into this study. All had a raised IgE to eggs (RAST test). Results to DBPCFC: positive in 69% in the egg exclusion group vs 67% control; and negative in 13% and 10% respectively (the remaining patients defaulted).	Egg exclusion diet vs Control (no specific dietary advice)	Outcomes at 4 Weeks: Body surface area affected (mean change) -8.7% vs -3.2%, p=0.04 (95% CI for mean difference in score between groups 0.1 to 10.9) vs Severity score (mean change) -9.4 (SD 12.3) vs	Source of Funding: none declared Children were not eating eggs as such, but in hidden forms such as pasta and cakes. All continued with topical treatment for AE during the study. Egg exclusion diet = exclusion of all foods containing eggs. Control = no specific advice on any particular item of food. Severity score = six clinical features assessed on a scale of 0-3, on 16

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					-3.3 (SD 10.5), p=0.05 (95% CI for mean difference between groups -0.1 to 12.3)	body sites (extent, erythema, oedema/papulation, oozing/crusts, dryness, lichenification). Body surface area was calculated using the rule of nines. EL=1- because only the 89% who completed the treatment period were analysed.
Majamaa H;Isolauri E; 1997 Feb 223	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 27 Extensively hydrolysed whey formula + Lactobacillus* N = 13 Extensively hydrolysed whey formula N = 14	Children aged 2.5-15.7 months with AE and a history suggestive of cow's milk allergy, confirmed by DBPC cow's milk challenge. Duration of exclusive and total breast-feeding were 2.8 months (range 2.1-3.5) and 5.9 months (4.5-7.2) respectively. Baseline median (IQR) SCORAD scores were 26 (17-38) in the intervention group and 21 (14-31) in the control group, p=0.33.	Extensively hydrolysed whey formula + Lactobacillus* vs Extensively hydrolysed whey formula	Outcomes at 1 Months: SCORAD (median score change) -11 (42%), p=0.008 vs baseline vs -2 (10%), p=0.89 vs baseline (no between-group analysis)	Source of Funding: Academy of Finland, Medical Research Fund EL=1- because of limited baseline data therefore cannot determine whether groups similar at baseline. Eczema lesions were treated with emollients and TCS. *5x10 (-8) colony forming units per gram, added to the whey formula. The quantity varied from 500-1000ml, depending on the age of the child. Otherwise, diet was 'normal for age'. Other parameters were also measured (data not reproduced here): faecal concentration of eosinophil cationic protein, alpha-antitrypsin, tumour necrosis factor alpha.
Isolauri E;Sutas Y;Makinen-Kiljunen S;Oja SS;Isosomppi R;Turjanmaa K; 1995 Oct 201	Study Type: Randomised Controlled Trial Evidence Level: 3	Total number of patients = 45 Cow's milk substitutes N = 45	Infants aged 4-8 months (mean age 6 months) who had AE and a positive reaction to a DB challenge with cow's milk, had not been breast-fed, and had needed a cow milk substitute formula for at least 6 months. Baseline SCORAD 17 in those receiving the whey substitute and 21 in the amino-acid formula group.	Cow's milk substitute (hydrolysed whey, n=22; or amino-acid derived formulae, n=23, as desired)	Outcomes at 8 Months: SCORAD (mean score change) -12 (71%) in those receiving whey and -17 (81%) with the amino-acid formula, p=0.001 vs baseline vs Weight	Source of Funding: Academy of Finland Additional dietary restrictions were made on the basis of history, skin tests, RASTs, and clinical challenge. These included no eggs and no cereal for 68% of the whey group and 65% of the amino-acid group.

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					'increased similarly' in both groups (no numerical data). The data were shown in graphs; weight increased in both groups in the first month of treatment, and continued to increase in the amino-acid group over the 9-month follow-up period. The pattern in the whey substitute group was less consistent, but weight at 9 months was about the same or worse than at baseline. In terms of statistical significant there is overlap of the 95% CI for the groups for weight. vs Length increased in amino-acid formula group but not in whey group, p=0.006 (no numerical data). Data were shown in graphs which show that length increased in both groups in the first month of treatment, and continued to increase in the amino-acid group over the 9-month follow-up period. The pattern in the whey substitute group was less consistent, but length at 9 months was about the same or worse than at baseline. In the graphs there is no overlap of the 95% CI for the groups for length which indicates statistically significant differences between groups.	Plasma amino-acid concentrations were compared with corresponding results in healthy age-matched infants who were breast-fed. Fasting morning plasma amino acid concentrations were taken and mean essential and branched amino-acid concentrations quoted. Data not reproduced here. Energy intake was similar in both groups. [EL=1-] Although described as randomised in the abstract, randomisation is not described elsewhere in the document. Additionally the interventions were given 'as desired', implying some degree of choice in the milk substitute given, which would nullify randomisation.
Glover MT;Atherton DJ; 1992 Apr [229]	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 26 House dust mite sensitisation N = 13 Placebo N = 13	Children aged 5-16 years (mean 10.26 years) with severe AE unresponsive to adequate treatment with emollients, mild TCS, ichthammol paste bandages, systemic antihistamines, and 'appropriate' elimination diets. All had positive skin prick reaction to Dermatophagoides pteronyssinus (a weal at least 4mm in diameter). 78% also had asthma, and 92% allergic	Tyrosine adsorbed glycerinated extract of D. pteronyssinus* vs Control (tyrosine suspension alone*)	Outcomes at 6 Months: Severity of erythema (mean score change) -45% vs -49%, p=0.643 for difference between scores at endpoint vs	Source of Funding: National Eczema Society/ Beecham's Pharmaceuticals *given by subcutaneous injection once a week for 6 weeks (dose increasing to a maximum of 400 Noon units); then given once a month for up to 6 months. Injections were given in hospital and followed

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
			rhinitis.		Severity of surface damage (mean score change) -47% vs -32%, p=0.907 for score difference at endpoint vs Severity of lichenification (mean score change) -43% vs -48%, p=0.685 for score difference at endpoint vs Parents assessment 62% better 31% same 8% worse vs 82% better 18% same 0% worse vs Adverse effects 6 redness at injection site vs Adverse effects 6 redness at injection site 1 faintness and dizziness 4 hours after injection	by medical supervision for at least 2 hours. Parameters measured fro severity were assessed using a scale of 0-3. Scores for erythema and lichenification were 'slightly higher' at the start in patients receiving active treatment. Skin prick tests were done at baseline and after 12 injections to variety of allergens. IgE also measured at baseline and after 12 injections.

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes and results	Comments
Galli E;Chini L;Nardi S;Benincori N;Panei P;Fraioli G;Moschese V;Rossi P; 1994 Jan 230	Study Type: Cohort Study Evidence Level: 2-	To evaluate the efficacy of an oral specific hyposensitisation therapy (to house dust mite) in children with AE and positive skin prick tests and/or RAST to house dust mite.	Total No. of Patients = 60 Children with AE and respiratory allergy (asthma or rhinitis), all given oral hyposensitisation therapy; had previously had a 6-week free diet of cow's milk and/or eggs N = 26 Children with AE only; all given oral hyposensitisation therapy N = 16 Children with AE exclusively, treated with conventional therapy N = 18	Children aged 0.5-12 years (mean 4.6 years) with AE and positive skin prick tests to house dust mite solutions and/or positive RAST for anti-house dust mite IgE.	Outcomes at 3 Years: 'Dermatitis score' (mean score change) -8.4 (54%), p=NS between groups	Funding: none declared Oral hyposensitisation therapy was randomised to the two groups who received this intervention. EL=2- because baseline characteristics were not given therefore it is not possible to determine whether groups were similar other than in the intervention. Clinical features of erythema, vesicles, fissuration, lichenification, and itching gives a score of 0-3 (absent-severe). Oral hyposensitisation therapy contained major (Der p1 and Der p11) and minor antigens of house dust mite. The dose was increased up to a final dosage of 250 'STU' (not defined) administered three times a week. Duration of immunotherapy was: mean 18.7 vs 16.3 months in the AE plus allergy group vs AE only group respectively. All children were treated with conventional therapy when needed, and used preventive measures to avoid the exposure to house dust mite. The % improvement was also reported but this was not defined.
Sanda T;Yasue T;Oohashi M;Yasue A;	Study Type: Cohort Study	To investigate the effectiveness and mechanism of action of an air-	Total No. of Patients = 30	Children and adults aged 9-75 years	Time to recurrence of symptoms (unspecified; mean [range])	Funding: none declared

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes and results	Comments
		cleaning system (clean room therapy) in HDM allergen-sensitive patients with atopic eczema.		(mean early 20s) with atopic eczema (score of 4.5 [scale not specified]) covering at least 18% of body surface area.		
1992 228	Evidence Level: 2-		Clean room therapy (patients had HDM allergen-specific IgE RAST score of 3 or higher) N = 30 Clean room therapy (HDM allergen-specific IgE RAST score of 0) N = 11 Control (common sickroom; and HDM allergen-specific IgE RAST score of 3 or higher) N = 10	All had a score of 0 for mold-specific (Candida) animal dander-specific and pollen-specific IgE RAST scores.	8.4 (2-34) vs 1.7 (1-4) vs 1.6 (1-3) months	Patients were hospitalised for treatment. Clean room therapy consisted of an air-cleaning system incorporating a HEPA filter; ventilation exchange of inside for outside air was conducted for about 10 minutes a day. Patients in the clean rooms were not allowed out except to go to the washroom/toilet. The ordinary 'sick room' used by the control group was identical in design to the clean room but without the air-cleaning system; patients were allowed free movement in and out of the room. There were two patients to every room. Use of hydrocortisone butyrate 0.1% and/or beclometasone dipropionate 0.025% was permitted. The statistical significance of changes in laboratory parameters and HDM particle counts were also reported (no numerical data) - not reproduced here. Patients were hospitalised for 3-4 weeks.
Devlin J;David TJ;Stanton RH; 1991 208	Study Type: Case series Evidence Level: 3	To describe the treatment and follow-up of children with AE treated at home with a diet eliminating all but six foods.	Total No. of Patients = 63 Few foods diet N = 63	Children aged 0.4-14.8 years (median 2.9 years) with AE, selected for the study either because of extensive (more than 30% skin surface area) skin involvement poorly responsive to conventional therapy	Severity change in median score: from 60 (20-240) to 40 (4-270), -33%, p<0.001. 39% had 'little or no improvement'. 52% had 20% or greater reduction in disease	Source of Funding: North Western Regional Health Authority Comments: The diet consisted of six foods: lamb, potato, rice, rice krispies, carrot and pear. Only water was permitted to drink.

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes and results	Comments
				or because of a 'clear history' of food intolerance (those with a food intolerance were already avoiding the foods concerned). 73% had a history of intolerance to 1-8 (median 3) foods, usually manifested as urticaria/angio-oedema, or exacerbation of AE.	severity score	If a child had a history of intolerance or dislike of one of the foods, a small number of alternatives were given instead. 20 were given a casein hydrosylate milk formula. All diets were supervised by a dietician. Parents asked to continue with usual treatment (although some changes were permitted if there was marked improvement or deterioration in the skin condition). If there was a 20% of greater improvement in disease severity score, then foods were reintroduced singly. Severity score = surface area x erythema score (0-3). It was also noted that 68% were followed up for '12 months or more. Regardless of the response to treatment, at one year the final outcome was very similar'.
Ehlers I;Worm M;Sterry W;Zuberbier T; 2001 Aug 215	Study Type: Case series Evidence Level: 3	To investigate whether sugar exacerbates atopic eczema.	Total No. of Patients = 30 Sugar (sucrose) elimination* N = 30	Children and adults aged 2-47 years (mean 25 years) with atopic eczema. Exclusions: those with diabetes and phenylketonuria.	Changed from 31.7 (13, 65) to 29.4 (8, 60) after the 1-week elimination diet, then +3.1 (-9, 15) after sucrose challenge, and -4.4 (-22, 2) after the placebo challenge.	Source of Funding: Charite Research Foundation Comments: *1-week elimination of sugar, sweets, and avoid regarding alternative sweeteners such as honey, maple syrup, and fruits. Aspartame was offered as a replacement sweetener. In the DBPCFC, 100g sucrose (40g for children aged under 6 years) was given +200mg

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes and results	Comments
						aspartame (so that both active and placebo challenges tasted similar). The placebo was 500mg aspartame (+200mg to ensure the same taste). Foods were added to a dessert.
Mehl A;Verstege A;Staden U;Kulig M;Nocon M;Beyer K;Niggemann B; 2005 Aug 191	Study Type: Case series/diagnostic Evidence level 3	To investigate whether a higher ratio of specific to total IgE would result in higher probability of symptomatic food allergy	Total No. of patients = 501 Children with suspected food allergy N = 501	Children aged 3 months to 16 years (median 13 months) with suspected food allergy (88% had atopic eczema)	Proportion of positivie tests results on food challenge: 49% to cow's milk, 66.5% egg, 35% wheat, 6% soya. Delayed 6% milk, 3% egg, 10% wheat, 8% soya. Both early and delayed reactions: 8% milk, 12% egg, 9% wheat, 5% soya. Total IgE ranged from 0.3-13.525 ku/l (median 94.3). Ratio of specific to total 0-91% (median 0.3%) for milk, 69.4% (median 1.7%) for egg, 70.7% (median 0) for wheat, and 15% (median 0) for soya. Significant correlation was reported for the outcome of food challenges for milk, egg, and wheat but not for soy. At the 95% predictive probability, for hen's egg a ratio of specific to total IgE of 19.1% had sensitivity of 10%, NPV 35.7%, and specificity and PPV of 100%. No predictive probabilities could be calculated for cow's milk, wheat or soya.	Source of Funding: None declared Comments: Antihistamines were withdrawn 72 hours before testing. TCS were allowed twice daily. Testing was only undertaken when eczema was controlled. Elimination diets were used 1 week before testingh. Food challenges (n=992) 74% were DBPCFC (placebo = neocate). Open challenges were used for children younger than 12 months who had a clear history of immediate type reactions. Increasing doses of foods were used (fresh milk, soyamillk, wheat powder, and raw hen's egg). Test positivie if 1 or more of the following: urticaria, angiodema, wheezing, vomiiting, diarrhoea, shock or exacerbation of eczema. IgE: to cow's milk, egg, wheat and soya. The lower detection limit was 0.35ku/l.
Hill DJ; Lynch BC 1982 May	Study Type: Case series	To investigate the effects of an elemental-based diet in children with severe atopic eczema.	Total No. of Patients = 10 Elemental diet	Children (age not stated) with severe generalised atopic eczema which was	Eczema scores fell in the 8 children who completed 6 weeks' treatment, and were significantly lower than at baseline, p<0.001. After resuming their usual diet for 6 weeks, scores	Source of Funding: None declared.

Bibliographic information	Study type and evidence level	Study aims/objectives	Number of patients	Patient characteristics	Outcomes and results	Comments
[213]	Evidence level: 3		(Vivonex-Eaton) for 2 weeks, then pumpkin, potatoes, zucchini, apples, pears, and pure vegetable margarine added for weeks 3-6. N = 10	persistent and unresponsive to topical treatment.	increased towards baseline, p>0.05 vs baseline. Adverse effects were not considered.	Comments: 2 children withdrew in the first week. The eczema score was calculated by adding severity (0-3) with extent (0-3, non-involving trunk and flexures), and use of TCS.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Study summary
Niggemann B, Reibel S, Roehr C, et al.; 2001[547]	Cohort Evidence level = 2	To identify the number of patients with food allergy but without IgE sensitivity.	n=139 Age 2 months – 11.2 years, median 13 months All children had atopic eczema.	Children with atopic eczema referred for food allergy investigation.	Positive reaction to DBPCFC	208 DBPCFCs undertaken, 111 were positive, of which 59 were early, 25 were late and 27 were combined early and late. 46 early reactions included urticaria All late and combined reactions were related to atopic eczema Allergens tested were cow's milk, egg and wheat. There were 52 +ve challenges to cow's milk, 38 to egg and 21 to wheat. There were 12 +ve tests with allergens that did not display high sIgE.	Retrospective review of consecutive referrals to allergy clinic.
Sampson H. 1983[548]	Cohort Evidence level = 2	To determine whether immediate reactions to food play a part in the pathogenesis of atopic eczema	n=26 age 16 months – 19 years, median 11 years all children with atopic eczema, serum IgE concentrations > 1000U/ml, history of possible food hypersensitivity, capable of cooperating with challenge procedures.		Diagnosis of food allergy	15 children had +ve challenge tests (23/104 tests) 21 tests provoked cutaneous reactions +ve challenges or convincing history of anaphylaxis were to egg (10), milk (4), peanut (3), wheat (3), soya (2), chicken (2) fish (1), chocolate (1), potato (1), rye (1)	Small study investigating concordance between skin tests and food challenge.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Study summary
Sampson H, McCaskill C.; 1985[549]	Cohort Evidence level = 2	As in study [548]	n=113, age 4 months – 24.5 years, median 6 years all had atopic dermatitis	Children referred for investigation of severe atopic eczema	Foods inducing reactions in DBPCFC	101/370 +ve food challenges in 56% of patients. Main allergens as derived by DBPCFC or convincing history were egg (44 challenges), peanut (20 challenges) and milk (11 challenges). Other allergens were soya, wheat, fish, chicken, pork, beef and potato.	
Burks A, James J, Hiegel A, et al.; 1998[550]	Cohort Evidence level = 2	To determine if screening for food allergy by skin prick testing can identify food allergy.	n=165, age 4 months – 21.9 years, median 49 months)	Patients attending allergy clinic with atopic eczema	Food allergy identified by DBPCFC	266 DBPCFC tests carried out, 83 were positive plus 12 identified by convincing history of anaphylaxis. All reactions occurred within 2 hours. Main allergens were peanut (27/44 challenges), milk (14/28 challenges). Other foods producing reactions were wheat, soya, cod, catfish, cashew, chicken, kidney bean, tomato, beef, other pulses and shrimp.	
Eigenmann P, Calza, A-M.; 2000[142]	Cohort Evidence level = 2	To report how food allergy diagnosis is made.	n=74, age 6 months – 16.3 years, median 2.5 years	Patients attending paediatric allergy or dermatology clinics with atopic eczema	Food allergy identified by CAP or DBPCFC	6 children underwent DBPCFC of whom 3 were allergic to milk and 2 to soya.	Retrospective review of consecutive referrals

Emollients and bandages

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Hindley D;Galloway G;Murray J;Gardener L; 2006 Feb 249	Study Type: RCT Evidence level: 1-	50 (45 analysed) Wet wraps n=28 Conventional treatment n=22 Exclusions: active skin infection; previous allergic reactions to proposed trial treatment; eczema predominantly on the face	Children with atopic eczema with moderate or severe atopic eczema (SCORAD scores >15) aged 4-27 months, median age 8 months in wet wraps arm and 14 months in conventional treatment arm	Intervention: Wet Wraps treatment initially applied daily for 24 hours a day over hydrocortisone ointment 1% (or more potent topical corticosteroid is required) for a week, followed by wet wraps 12 to 24 hours a day depend on progress assessed by the research nurse. When wet wraps was used for 12 hours a day the hydrocortisone 1% and emollients were used as required during the non-wet wrap peroid Concomitant treatment: 1. a sedative antihistamine as required 2. oral antibiotics as required	Follow-up period: 4 weeks Outcome Measures: 1) Disease severity (mean change in SCORAD scores) 2) Quantity of topical corticosteroids used 3) Concomitant treatments (used by % children) 4) Nurse/carer ratings in a) difference in eczema control (% better or much better) b) ease of use of treatments (% easy to very easy to use) c) how easy to tolerate (% easy or very easy)	1) -29 (55%) vs -24 (59%) 'Effect of allocation (effect of intervention from linear regression model after adjustment for baseline) -3.4 95% CI -12.2 to 5.5, p=0.44' 2) Mean difference -0.56g/day, 95% CI -1.9 to 0.8 g/day, p=0.404 3) Sedative antihistamines 13% vs 14% Antibiotics 22% vs 0%, difference 22%, 95% CI 5% to 42%, p=0.05 4a) nurse rating 65% vs 59%, p=0.672 carer rating 70% vs 64%, p=0.758 4b) carer rating 39% vs 73% p=0.036 4c) carer rating 48% vs 67% p=0.239	Funding: NHS research and development fund (North West) The study was conducted in a secondary care paediatric department. [EL=1-] because the study was underpowered to detect clinically significant differences (the sample size in each group was only half that needed to ensure 80% power at the 0.05% level of statistical significance), the 'education' nurses were not blind to the treatment allocation, and only those who completed treatment were analysed. Withdrawal rates were 5 (22%) in the wet wrap group vs 0 with control, p=0.057. Withdrawals were due to non-compliance. One child in the wet wrap group received a potent topical corticosteroid (no further details) from days 4-7, and was subsequently withdrawn from the study

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
				Comparison: Conventional treatment: emollients applied at least 3 times a day and as required use of hydrocortisone ointment 1% twice a day (or use more potent topical corticosteroids if required) for 4 weeks			
Beattie PE;Lewis-Jones MS; 2004 Jul 326	Study Type: RCT Evidence level: 1+	19 children Wet wraps n=10 Conventional treatment n=9 Exclusions: children requiring more potent topical corticosteroids than hydrocortisone 1%; use of oral steroids or antibiotics within 2 weeks; concurrent ues of systemic or alternative therapies	Children with atopic eczema affecting 30% or more of their body surface area, without infectious evidence. Age 4 months to 3 years, mean 1.77 years in wet wraps arm, and 1.44 years in conventional treatment arm Baseline SASSAD scores 28 vs 29.9	Intervention: Hydrocortisone 1% applied once in the morning for 2 weeks, with wet wraps applied twice daily for the first week and only at night for the second week. Only an emollients was used during the third week. Emollients could be used as required for the whole duration of the study. One finger-tip unit was spread over two hand areas. A 20-min time delay between use of steroids and emollients Comparison: Hydrocortisone 1% applied twice daily for 2 weeks, followed by emollients only for the	Follow-up period: Duration of treatment 3 weeks Outcome Measures: 1) SASSAD scores a) mean change from baseline at week 2 b) mean change from baseline at week 3 2) Quantity of topical corticosteroids used (median) 3) Quantity of emollients used (median) 4) Quality of life a) IDQOL (median change in scores at week 3) b) DFI (median change in score at week 3) 5) Adverse effects	1a) -10.3 (37%) vs -15.7 (53%) 'mean fall in SASSAD was 8 more without wet wraps, 95% CI -18 to 2, p=0.11) 1b) -11.4 (41%) vs -15.7 (53%) 2) week 1: 14.9g vs 24.8g week 2: 9.3g vs 18.9 g, p=0.10 3) week 1: 285.5 g vs 199.9 g week 2: 224.5 g vs 221.5 g week 3: 200.3 g vs 257.7 g 4a) -2 vs -7, 95% CI for difference -10 to 3, p=0.24 4b) -2 vs -5, 95% CI for difference -14 to 2, p=0.42 5) 2 (20%) vs 0 folliculitis withdrawals: 2 (20%) vs 2 (22%) due to folliculitis, unable to attend vs non-compliance, treatment failure.	Funding: The Tayside University Hospitals Trust grant scheme The study was described as a pilot RCT. Head and neck excluded from wet wrap therapy. Within the quality of life assessment, changes in sleep scores were also reported (improvements in both groups), but no between-groups analysis.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
				third week. Emollients could be used as required for the whole duration of the study.	and withdrawals		
Wolkerstorfer A;Visser RL;De Waard van der Spek FB;Mulder PG;Oranje AP; 2000 Nov 328	Study Type: Cohort Non-randomised controlled trial Evidence level: 2-	31 children Group 1: 50% dilution of fluticasone propionate (FP) 0.05%, n=18 Group 2: a side-to-side 10%, 25% and 50% dilution of FP 0.05% for one week, then 10% dilution for one week, n=5 Group 3: 0% (emollient), 5%, 10% or 25% dilution of FP 0.05%, n=8	Children with severe refractory atopic eczema aged 5 months to 13 years, mean age not reported. SCORAD score >40 in 29 (94%)	Intervention: Group 1: 50% dilution of FP cream under wet wrap treatment for 2 weeks Group 2: different dilution (10%, 25% and 50%) of FP cream under wet wraps treatment for body symmetrically eczema for 2 weeks Group 3: different dilution (0% (emollient), 5%, 10% and 25%) of FP cream under wet wraps treatment for 2 children in each strength for 2 weeks Comparison: The serum corticol levels before and after wet wrap treatment in different dilution of FP strength groups	Follow-up period: Duration of treatment: 2 weeks Outcome Measures: 1) Mean serum cortisol levels (SD) a) Group 1 b) Group 2 c) Group 3 2) Adverse effects a) Group 1 b) Group 2 c) Group 3	1a) Overall, no significant decrease in cortisol levels at week 2, p=0.24. Levels were 'temporarily below the normal range' (0.2-0.8 micromol/l) in 3 (17%) children 1b) 0.45 (0.17) micromol/l at week 2 vs 0.42 (0.16) at baseline 1c) levels were below the normal range in 2/8 children (0.03 and 0.09 micromol/l). Serum cortisol levels vs FP quantity per body surface area (microgram per m2) for each of the 8 patients: 0.28 vs 0 0.46 vs 0 0.55 vs 564 0.39 vs 728 0.36 vs 835 0.09 vs 957 0.03 vs 1129 0.33 vs 2071 2a) 30% (6/18) upper respiratory tract infection 30% (6/18) folliculitis 5.5% (1/18) herpes simplex infection 5.5% (1/18) diarrhoea 5.5% (1/18) itching	Funding: none declared. Tubifast was the bandage used. The cream was applied to the whole body. The bandage was rewetted every 2 hours with water using aspary bottle. Cortisol was measured at 9 o'clock in the morning in groups 1 and 2, at baseline and after 2 weeks. In group 3 serum cortisol and urinary timed morning cortisol/creatinine ratio was measured daily at 6 o'clock in the morning for the first week of treatment. SCORAD scores were also measured, but only selected numerical data were reported; results were mainly presented in graphs. The proportions with mild, moderate and severe atopic eczema were also reported, but the method of classification was not described.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						2b) 40% (2/5) upper respiratory infection 40% (2/5) folliculitis 20% (1/5) abdominal pain 20% (1/5) itching 2c) 63% (5/8) folliculitis 12.5% (1/8) balanitis 12.5% (1/8) furunculosis	
Grimalt R;Mengeaud V;Cambazard F;Study Investigators' Group.; 2007 [248]	Study Type: RCT Infants under 12 months randomised to topical corticosteroid plus emollient or alone Evidence level: 1+	173 randomised; 82 to control, 91 to treatment; 162 analysed, 4 lost to follow up in control group, 5 in treatment group. 2 infants randomised to treatment group did not meet inclusion criteria.	Infants less than 12 months old with moderate to severe atopic dermatitis (SOCRAD 20-70, mean 35 at baseline) Excluded if SOCRAD<20 or SOCRAD >70 or if emollients or topical corticosteroids had been used in week prior to commencement of study. Infants older than 12 months were excluded as well as any with history of allergy to a product constituent or medical problems likely to interfere with AD evaluation.	Intervention: Topical corticosteroid plus emollient Comparison: Topical corticosteroid alone. Topical corticosteroids used were micronized desonide 0.1% cream or desonide 0.1% cream Emollient used was an emollient emulsion (Exomega) containing evening primrose oil and oat extract.	Follow-up period: 6 weeks Outcome Measures: Primary outcomes: consumption of high-potency corticosteroids, consumption of moderate-potency corticosteroids. Secondary outcomes: severity of atopic eczema (SOCRAD score), quality of life (French version of IDQoL and DFI), tolerance and safety.	Mean weight of high-potency corticosteroid consumption after 6 weeks: 14.7g (no emollient), 8.56 (emollient) (p=0.025) Mean weight of moderate-potency corticosteroid consumption after 6 weeks: 8.03g (no emollient), 7.43 (emollient) (p=0.92) No significant difference in SOCRAD score was found between the treatment groups at 6 weeks. No significant differences in quality of life were found between treatment groups. 2 patients suffered severe adverse effects and were not included in the analysis.	Data reported at 3 weeks but not reproduced here. Topical corticosteroid prescribed according to investigators' regular practice.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Giordano-Labadie F; 2006 235	Study Type: RCT Evidence level: 1-	Total: 76 Emollient: 37 No emollient: 39	Children aged 6 months to 12 years. SCORAD < 35	Intervention: Emollient used twice daily Comparison: Emollient vs. no emillient	Follow-up period: 8 weeks Outcome Measures: SCORAD, pruritus, xerosis, quality of life (CLQI)	Emollient group: CLQI reduction: 0.84 (p=0.001) SCORAD: 59% reduction (p>0.05) pruritus: 66% reduction (p<0.0001) xerosis:69% reduction (p<0.01) No emollient group: CLQI reduction 0.41 (p=0.17) SCORAD: 49% reduction (p>0.05) pruritus: 42% reduction (p>0.05) xerosis:36% reduction (p<0.01) p<0.01 for difference between the two groups on pruritus and xerosis.	No description of randomisation, concealment, dropouts.
Schnopp C;Holtmann C;Stock S;Remling R;Folster-Holst R;Ring J;Abeck D; 2002 250	Study Type: RCT Left-right side comparison Evidence level: 1-	20	Children aged 2-17 years ('medium' age 7.2 years), presenting at outpatients with exacerbation of atopic eczema, and skin lesions symmetrically affecting either inside of elbows or back of knees. Medium SCORAD score 52.6 (SD 16.9), range 21.5-82.2	Intervention: Mometasone furoate 0.1% covered by wet wraps (n not stated) Comparison: Vehicle covered by wet wraps (n not stated)	Follow-up period: Duration of treatment, 5 days Outcome Measures: 1) SCORAD 2) Transepidermal water loss (change from baseline) 3) S aureus skin counts	1) No numerical data reported; data presented in graphs only. Statistically significantly greater reduction in mometasone group claimed, p<0.01 2) -16 (44%) mometasone vs -12.5 (36%), p=NS 3) Data not reported	Funding: Essex Pharmaceuticals Treatment given as hospital inpatients.
Pei AYS;Chan HHL;Ho KM; 2001 327	Study Type: RCT Evidence level: 1-	40 randomised, 27 completed treatment and analysed Fluticasone propionate	Children aged 1-15 years with atopic eczema, attending a paediatric outpatient clinic. Active disease despite treatment with a moderately potent topical corticosteroid	Intervention: Group 1: Fluticasone propionate 0.005% (diluted to 10% strength with petrolatum), for 4 weeks	Follow-up period: Outcome Measures: 1) Disease severity score (change in median at week 4; p vs baseline)	1) (group 1 vs 2 vs 3 vs 4 respectively) -6.50 (18%) p=0.091 -19.0 (46%) p=0.078 -24.0 (60%) p=0.018 -46.5 (77%) p=0.050	Funding: none declared [EL=1-] only completers analysed. *Disease severity score takes account of 6 signs measured over 8 areas, using a score of 0-3 (0 none to 3 severe, and giving a maximum score of 144. The 6

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
		0.005% (diluted to 10% strength with petrolatum) n=21 Mometasone furoate 0.1% (diluted to 10% strength with petrolatum) n=19 Exclusions: treatment with systemic corticosteroids, immunosuppressants, Chinese herbal medicine or antibiotics within 6 weeks; other skin conditions or infections	plus soap substitutes and emollients. Minimum disease severity score 40/144*. Baseline median scores 36.5, 41, 40, and 60.50 in groups 1, 2, 3, 4 respectively. Disease extent scores 54 vs 70.50 (groups 3 and 4 only) Topical skin treatment was standardised to emulsifying ointment as a soap substitute, petrolatum as emollient, and flucinolone acetonide 0.005% cream, applied twice daily	Group 2: Mometasone furoate ointment 0.1% (diluted to 10% strength with petrolatum), for 4 weeks Comparison: Group 3: Fluticasone propionate 0.005% (diluted to 10% strength with petrolatum), for 2 weeks, then under wet wraps for 2 weeks Group 4: Mometasone furoate ointment 0.1% (diluted to 10% strength with petrolatum), for 2 weeks, then under wet wraps for 2 weeks In all groups, petrolatum was applied to non-affected areas	2) Disease extent score (change in median at week 4; p vs baseline) 3) Subjective assessment of impact of atopic eczema on daily life (scale o-3, where 3=highest impact), p vs baseline	2) Groups 3 and 4 only -30.0 (56%) p=0.028 -48.0 (68%) p=0.025 3) Groups 3 and 4 only +1 (6%) p=0.671 -3.5 (18%) p=0.011	signs are erythema, oedema/papulation, oozing/crusting, excoriation, lichenification, dryness). Disease extent score estimates the body surface area involved; 8 areas are evaluated, with contributions of 9% each for three areas, 18% for four, and 1% for one. Patients initially received the TCS for 2 weeks, then if less than 50% improvement in their condition, they were further randomised to continue with the same treatment alone, or the same under wet wraps. At bedtime, patients applied medicated ointment to affected areas after a bath, then tubifast dressings soaked in warm water were placed over the affected areas. A second, dry, layer was placed over the wet layer. Dressings were left on overnight beofre removal in the morning. Ten patients achieved 50% or greater improvement at week 2 therefore did not enter the second half of the study. Three children withdrew from the study, 1 unable to tolerate the fluticasone wet wrap, 2 stopped after first week and dropped out because they 'felt eczema was static'.
Lucky AW;Leach AD;Laskarzewski P;Wenck H; 1997 Jul [245]	Study Type: Cohort Non-randomised comparative trial Evidence level: 2-	25 Exclusions: topical corticosteroid creams not indicated; hypersensitivity to corticosteroids.	Children with mild to moderate atopic eczema, and clinically evident atopic eczema present symmetrically either on both, antecubital or popliteal fosssae or on matching areas on the extensor surfaces of the arms, legs, trunk, or cheeks. Age 3-15 years, mean 7.8 years.	Intervention: Hydrocortisone cream 2.5% plus emollient (Eucerin), both applied once daily Comparison: Hydrocortisone cream 2.5% applied twice daily	Follow-up period: Duration of treatment, 3 weeks Outcome Measures: 1) Signs and symptoms of eczema (mean change in scores at 3 weeks, on scale of 0-3, none to severe) a) erythema b) scaling/crusting c) excoriation d) lichenification e) burning/stinging	1a) -1.4 (73% vs -1.44 (75%) 1b) -1.48 (77%) vs -1.52 (81%) 1c) -1.52 (83%) vs -1.4 (83%) 1d) -1.2 (83%) vs -1.24 (86%) 1e) -1.04 (100%) vs -1.0 (100%) 1f) -2.12 (95%) vs -2.24 (93%) 1g) -1.44 (67%) vs -1.56 (75%) p>0.545 for 'rates of improvement' 2) -66% vs -68% (unclear whether this applies to the total area of all lesions)	Funding: none declared Investigator was blind to assigned treatment. [EL=2-] because unclear whether groups were similar at baseline - only baseline scores for global condition shown, no further details about the children. Moisturising characteristics of the emollient were also investigated (satisfaction, ease of use) but incomplete data reported therefore data not reproduced here. The quantities of TCS used in each group were not reported.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
					f) itching g) global 2) Mean size of least and greatest diameters of lesions (millimetres squared)	p>0.98 between groups	
Harper J; 1995 241	Study Type: RCT Evidence level: 1-	30 randomised, 26 analysed Exclusions: concurrent use, or use within 2 weeks, of systemic or topical antibiotics or oral corticosteroids	Children aged 1-9 years (mean 4.5 years) with atopic eczema displaying features of recurrent infection and/or frequent exacerbations. 88% had at least three exacerbations in their eczema during the 12-month period prior to study entry.	Intervention: Oilatum bath emollient. 15ml was added to 8 inches of bath water, the child soaked for 10-15 minutes. Comparison: Oilatum Plus bath emollient. 15ml was added to 8 inches of bath water, the child soaked for 10-15 minutes.	Follow-up period: Duration of treatment, 4 weeks Outcome Measures: 1) Mean change in total clinical score* from baseline 2) Global impression scale, global change scale, self-reported diary 3) Adverse effects	1) 2.7 (SEM 2.6) Oilatum vs 9.2 (SE 2.9) Oilatum plus. Assumed these are redcutions. No baseline scores reported, although it was reported that the change from baseline in the Oilatum Plus group was significant, p<0.05 2) Although described as outcomes, no numerical data reported. 'No significant difference' between groups claimed. 3) n=4 vs 3 pruritus	Funding: none declared [EL=1-] because no baseline data for main outcome, and fewer analysed than randomised. Single centre, double-blind cross over study. Each bath additive was used daily for 4 weeks, separated by a 2-week washout period. Emulsifying ointment or aqueous cream were used as a soap substitute in all cases, and any pre-study topical corticosteroid therapy was continued unaltered during the study. *total clinical score takse account of 10 signs and symptoms of eczema, and the area of the body affected; total score 100.
White MI;Batten TL;Ormerod AD; 1994 244	Study Type: Cohort within patient left-right side (arm) comparison Evidence level: 2-	9 Exclusions: clinical infection; known allergy to emollient; atopic condition requiring systemic corticosteroid therapy	Children with chronic stable atopic eczema attending a paediatric outpatient clinic. Aged 5 months to 13 years. Baseline clinical scores (presented in graphs only) ranged from 1 to 7	Intervention: Daily use of bath emollient (one arm soaked in a basin of warm water with 1ml Oilatum added, for 15 minutes/day) plus usual care (weekly bathing in bath containing 15ml emollient, twice daily application of emollient and topical corticosteroid, use of 3% aqueous emulsifying was as a	Follow-up period: Duration of treatment, 4 weeks Outcome Measures: 1) Mean difference in clinical score at week 4 2) Mean difference in change in clinical score over duration of study	1) 1.25 (SE 0.88), 95% CI -0.84 to 3.34 Mean scores only presented in graphs. 2) 0.93 (SE 0.32), 95% CI 0.21 to 1.66, p=0.019	Funding: none declared Examiner was unaware of which arm was being soaked in bath emollient daily Clinical score takes account of extent and severity of atopic eczema. Maxium score not stated

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
				soap substitute Comparison: Usual care (weekly bathing in bath containing 15ml emollient, twice daily application of emollient and topical corticosteroid, use of 3% aqueous emulsifying was as a soap substitute)			
Muzaffar F, Hussain I, et al 2002 246	Study Type: Cohort Evidence level: 2-	50 (a left-right comparison)	Children with mild to moderate atopic eczema (SCORAD scores 15-40, mean approximately 20). Mean age 3.5 (SD 2.5), no range reported.	Intervention: Betamethasone valerate 0.1% ointment applied in the morning to affected areas, and emollient applied in the evening (Oilatuma) Comparison: Betamethasone valerate 0.1% ointment applied twice daily to affected areas	Follow-up period: Duration of treatment, 4 weeks Outcome Measures: 1) SCORAD (mean change in score from baseline) 2) Adverse effects	1) -17.2 (88%) vs -17.5 (88%) 'no significant difference between groups' (no p value reported) 2) None were reported during the trial	Funding: none declared, although the emollient cream was provided by Stiefel Laboratories ltd. [EL=2-] because no baseline data were reported, therefore cannot tell whether groups were similar in all aspects other than the intervention. The quantities of TCS used in each group were not reported.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
Tang WYM;Chan HHL;Lam VMF;Chong LY;Lo KK; 1999 [330]		Intervention: Wet wraps treatment with mometasone furoate 0.1% once daily for 2 weeks, diluted to 10% or 15% using emulsifying ointment (strength used depended on age and disease severity). Mometasone was applied to the affected areas and emulsifying ointment to all areas of dry skin of the body and limbs as an emollient. Wet wraps were worn for 10-12 hours per day. Comparison: N/A	12 Exclusions: systemic corticosteroid treatment, Chinese herbal medicine, or systemic immunosuppressant therapy in the preceding 3 months; extensive oozing or clinically infected eczematous lesions	Children with severe atopic eczema who failed to respond to at least 2 weeks' treatment with emollients and topical corticosteroids. Aged 3-12 years, mean 8.5 years.	1) Clinical severity score (0-3, applied to 5 clinical signs/symptoms, erythema, papulation/oedema, excoriations, lichenification, dryness), mean change 2) Self-assessment score (0-3, applied to 4 symptoms, mood disturbance, itchiness, sleep loss, social perturbation), mean change 3) 'early morning' plasma cortisol levels (n=8) 4) Adverse effects folliculitis	1) -7.5 (73%) 2) -6.2 (72%) 3) Within normal range in 7 of 8 children (166-773 nmol/l); below lower limit in 1 child (139nmol/l). Change from baseline not reported. 4) 25% (n=3) folliculitis 25% 'tight sensation' 8% itchiness 8% cool sensation 8% hot and wet sensation	Funding: none declared Dressings used were tubifast and tubigrip; 10 used tubigrip alone, 1 tubifast alone, and 1 used both. Parents made up the diluted product at home, having been provided with the weighed ingredients to make a fresh product every night. A 10% dilution was used in 4 children, and a 15% dilution in 8.
Cork MJ; 1998 [247]	EL=3	Intervention: Regimen 1: Fluprednidene-21-acetate applied twice daily days 1 and 3, emollients applied twice daily day 2 (repeated until day 21) Regimen 2: Fluprednidene-21-acetate applied twice daily days 1 and 4, emollients applied twice daily days 2-3 (repeated until day 21) Regimen 3: Fluprednidene-21-acetate applied twice	44	It is not clear whether the patients were children or adults. They had atopic eczema. No other demographic details.	1) Severity 2) Quantity of TCS used	1) No numerical data. Reported that the reduction in severity was similar in the four groups. Not stated how severity was measured. 2) The group using emollient for most days used 75% less TCS than the control group (TCS only).	This was a DB left-right side comparison.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
		daily days 1 and 5, emollients applied twice daily days 2-4 (repeated until day 21) Comparison: Fluprednidene-21-acetate applied twice daily, wihout emollients					
Chamlin SL;Kao J;Frieden IJ;Sheu MY;Fowler AJ;Fluhr JW;Williams ML;Elias PM; 2002 Aug [68]	EL=3	Intervention: Moisturising cream three times daily plus desonide 0.5% lotion applied twice daily (left side of body) To standardise a cleansing regimen, patients were also instructed to use a nonmedictaed cleansing bar (cetaphil) Comparison: Control group (desonide 0.5% lotion applied twice daily, used on right side of body) To standardise a cleansing regimen, patients were also instructed to use a nonmedictaed cleansing bar (cetaphil)	24	Patients aged 6 years and above with a 'confirmed diagnosis' of mild-to-moderate atopic eczema, having erythema, dryness or scaling, and pruritus on both sides of their body.	1) Symptom scores (7 signs or symptoms*, marked out of 9; maximum scores 63) 2) Global assessment of improvement (clear=100% clearance except for residual discolouration; marked improvement=75-99% improvement; definite improvement 50-74% improvement; minimal improvement =25-49% improvement;no change; and exacerbation 3) Tolerability	No numerical data for any outcome; data shown in graphs only	Funding: Galderma Laboratories Inc., Fort Worth, Texas. Target lesions were identified on both sides of the body; mirror lesions were preferred but not required. *erythema, dryness or scaling, pruritus, excoriations, lichenification, oozing or crusting, and indurations or papules. Scale 0-9: 0=none, 1-3=mild, 4-6=moderate, 7-9=severe
Cork MJ;Timmins J;Holden C;Carr J;Berry V;Tazi-Ahnini R;Ward SJ; 2003 [236]	EL=3	Intervention: Aqueous cream (used by 71%) Comparison: 'other' emollients (14 used; which not specified)	100	Children with atopic eczema aged 1-16 years attending a paediatric dermatology clinic. No further demographic details.	Proportion reporting an immediate cutaneous reaction (a report of one or more of burning, stinging, itching, and redness developing within 20 minutes of applying an emollient to the child's skin)	56.3% with aqueous cream 17.8% immediate cutaneous reactions per episodes of exposure (111 for 622 episodes Difference between aqueous cream and all other emollients grouped together	Funding: none declared. An anonymised form was completed from the children's notes and during clinic visits

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
						statistically significant, p<0.001	
Whitefield M; 1998 [240]	EL=3	Intervention: Dermol 500 lotion, applied to the affected areas as required; could be used in the shower or bath, and instead of ordinary soap or shower gel. Comparison: N/A	40 (39 completed)	Children aged 20 months to 13 years (mean 6 years) already receiving treatment for eczema/dermatitis and known to require emollients to manage their dry skin condition. Exclusions: acute secondary skin infection (exudative dermatitis); known or suspected history of intolerance or skin sensitivity to any of the ingredients e.g. benzalkonium chloride or chlorhexidine hydrochloride	1) Itching 2) Dryness 3) Satisfaction 4) Ease of use (cosmetic acceptability, n=34 [87%]) 5) Satisfaction with the effectiveness of the lotion as a soap susbstitute (in 27 who used the product in this way) 6) Adverse effects	1) Itching of limbs/trunk (n=37): 84% better, much better or completely better, 16% unchanged. Itching of face/neck (n=21): 86% better, much better or completely better, 14% unchanged. 2) Dryness of limbs/trunk (n=39): 87% better, much better or completely better, 13% unchanged or worse. Dryness of face/neck (n=21): 81% better, much better or completely better, 19% unchanged. 3) Overall effectiveness described as excellent, very good or good by 95%, and poor by 5% Of 79 comparisons with emollients used previously 72% ranked dermol 500 as better or much better, 23% 'were ambivalent', and 5% worse or much worse. 4) 24% excellent 41% very good 35% good Of 79 comparisons with emollients used previously 77% ranked dermol 500 as better or much better, 15% 'were ambivalent', and 8%	Funding: none declared (author's address Dermal Laboratories Ltd). Patients continued with their other systemic or topical treatments. Dryness of the skin assessed by visual inspection; severity of itching assessed using indicators such as the overall level of distress being caused to the child and by the intensity and frequency of scratching.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
						worse or much worse. 5) 4% excellent 15% very good 63% good 19% satisfactory 6) No adverse effects were reported.	
Ling TC;Highet AS; 2000 [243]	EL=3	Intervention: An antiseptic bath oil emollient containing benzalkonium cholride (6%) and triclosan (2%) (Oilatum Plus) Comparison: none	7 (case reports), 4 of whom were children age under 12 years	Patients with atopic eczema who had developed irritant reactions to an antiseptic bath oil emollient.	Adverse effects reported by each case	1) A 6.5 year old with infected atopic eczema (other treatments; antibiotics and topical corticosteroids): on first exposure to oilatum plus, developed an erythematous desquamating rash, affecting particularly the skin flexures of the groin. Half a capful had been used in a standard sized bath filled to half the depth. Previously used oilatum (plain) with no adverse effects 2) An 11-month old child with an infective episode that settled with potent topical steroids and oilatum plus.After 2 weeks of daily use of oilatum plus used according to the instructions, he gradually developed areas of dry, non-pruritic desquamation behind his knees. This resolved after oilatum plus was stopped. 3) A 2-year old girl presented with mild, infected atopic eczema for which she was prescribed oilatum plus and mild topical steroids. She gradually developed an	Funding: none declared.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
						irritant reaction to oilatum plus over several months, affecting the skin flexures, including the groin and the skin under the plastic of her disposable nappy. Her mother had been using an excessive amount of oilatum plus; two capfuls to only 5cm of water in a standard sized bath. The reaction settled following a change to a plain bath emollient. 4) A 2-year old boy with atopic eczema managed with emollients, topical steroids, antiseptic bath emollients and wet wrapping. He had an exacerbation of his atopic eczema while using oilatum plus; in an attempt to hasten his recovery, his mother had started to add extra capfuls of oilatum plus to the bath, after which his face was washed with the bath water. He developed erythema and scaling around his mouth and on his trunk which was worse on the skin flexures (but less itchy than his usual atopic eczema). Subsequent use of oilatum plus at the correct concentration was well tolerated with no adverse reactions.	

Topical corticosteroids

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Thomas KS;Armstrong S;Avery A;Po AL;O'Neill C;Young S;Williams HC; 2002 Mar 30 254	Study Type: RCT Double-blind Evidence level: 1+	207 Exclusions: severe eczema	Children with mild or moderate atopic eczema, 84% of children came from general practices, and 15% from a general hospital outpatient clinic (including 13 general practices and a teaching hospital). Age 1-15 years, mean 5 years in the HC group vs 6 years in the betamethasone group	Intervention: Betamethasone valerate 0.1% applied twice daily for 3 consecutive days, followed by a base emollient only (white soft paraffin) for 4 days (n=104 Comparison: Hydrocortisone ointment 1% applied twice daily for seven consecutive days (n=103)	Follow-up period: 18 weeks Outcome Measures: 1) Number of scratch-free days (n evaluated 198; median with IQR) 2) Number of relapses (n=165) 3) Number of undisturbed nights (n=165) 4) Mean (SD) change in Children's Life Quality index (n=168) 5) Mean (SD) change in Dermatitis family impact (n=169) 6) Adverse effects 7) Withdrawals (dropped out or resorted to concurrent treatment)	1) Potent vs mild: 117.5 (99.3 to 125.0) vs 118.0 (99.8 to 124.0), Difference: 0.5 (95% CI -3.0 to 2.0, day), p =0.68 2) 1.0 (0.0 to 3.0) vs 1.0 (0.0 to 3.0) Difference:0, p = 0.66 3) 121.0 (101.3 to 126) vs 123.0 (109.5 to 126) Difference: 2.0 (95% CI 0.0 to 2.0), p=0.53 4) -1.9 (3.0) vs -2.4 (4.0) Difference: -0.5 (95% CI -1.52 to 0.62) p=0.41 5) -0.6 (2.2) vs -0.5 (2.4) Difference: -0.1 (95% CI -0.60 to 0.80), p=0.78 6) Total 18 children reported adverse events (8.7%) 5% vs 9% worse symptoms 2% vs 0% spots/rashes 1% vs 0% hair growth 1% vs 0% viral encephalitis Skin thickness was measured by ultrasound in 51%: Baseline: 0.91 mm (mild arm), 0.99 (potent arm);	Funding: NHS R&D programme (Trent). Most outcomes were evaluated for the community population only (n=165). The total quantities of topical corticosteroids used during the trial were reported but only for 42% of the children.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						Mean change: -0.04 mm (SD 0.11mm) for mild arm, -0.05 mm (0.14) potent. 7) 25% vs 36%, mean difference 11%, 95% CI -3 to 25, p=0.19)	
Green C;Colquitt JL;Kirby J;Davidson P;Payne E; 2004 [288]	Study Type: Systematic review - meta-analysis HTA Evidence level: 1++	10 RCTs (data for children from 3 RCTs; two published and one from a manufacturer's submission to the NICE technology appraisal programme). Refer to evidence tables for Richelli 1990[287] for details of the first RCT Data for RCTs 2 and 3 are reproduced from the HTA because data for children are not published elsewhere	RCT2 Children with at least moderately severe eczema (score of 6 or more from a maximum of 9 for erythema, pruritus and thickening). RCT 3 (unpublished) Children with at least moderately severe eczema (score 7 or more but scale not described fully). Age range 1-12 years (subgroup of RCT involving children and adults)	Intervention: RCT2: Fluticasone propionate cream 0.05% applied once daily, n=63 RCT 3: Fluticasone propionate ointment 0.005% applied once daily, n=63 of 123 were children Comparison: RCT2: Fluticasone propionate cream 0.05% applied twice daily, n=63 RCT 3 Fluticasone propionate ointment 0.005% applied twice daily, n=57 of 122 were children	Follow-up period: RCT 3 Duration of treatment, 4 weeks (or less if eczema cleared sooner) Outcome Measures: RCT2 1) Global assessment, where success='cleared', 'excellent' or 'good'; and failure = 'fair', 'little' or 'worse' 2) Adverse events RCT 3 1) Global assessment, where success='cleared', 'excellent' or 'good'; and failure = 'fair', 'little' or 'worse' 2) Patients' self-assessment of success: success= totally, greatly, or moderately improved; failure = slightly improved, not changed, worsened or greatly worsened 3) Adverse events	RCT2 1) 86% once daily vs. 891% twice daily success, difference 3% (95% CI -15.5 to 9.6), p = 0.644 2) 37% vs 35% reported adverse events 24% vs 17% were possibly related to treatment, predominantly signs or symptoms relating to skin or their eczema RCT 3 1) 77% once daily vs. 91% twice daily success, difference 13.5% (95% CI 0.6 to 26.4), p = 0.048 2) 72% vs. 91% success, difference 18.6% (95% CI 5.0 to 32.3), p=0.011 3) 49% vs 40% reported adverse events 8% vs 17% were possibly related to treatment, but no details of these adverse events were reported.	Funding of RCT2: Glaxo. Funding of RCT3: not stated. Manufacturer (GlaxoSmithKline) assumed Refer to evidence tables for Richelli 1990[287] for details of RCT 1
Green C;Colquitt	Study Type:	10 RCTs	RCT2	Intervention: RCT2:	Follow-up period: RCT 3	RCT2	Funding of RCT2: Glaxo.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
JL;Kirby J;Davidson P;Payne E; 2004 [288]	Systematic review - meta-analysis HTA Evidence level: 1++	(data for children from 3 RCTs; two published and one from a manufacturer's submission to the NICE technology appraisal programme). Refer to evidence tables for Richelli 1990[287] for details of the first RCT Data for RCTs 2 and 3 are reproduced from the HTA because data for children are not published elsewhere	Children with at least moderately severe eczema (score of 6 or more from a maximum of 9 for erythema, pruritus and thickening). RCT 3 (unpublished) Children with at least moderately severe eczema (score 7 or more but scale not described fully). Age range 1-12 years (subgroup of RCT involving children and adults)	Fluticasone propionate cream 0.05% applied once daily, n=63 RCT 3: Fluticasone propionate ointment 0.005% applied once daily, n=63 of 123 were children Comparison: RCT2: Fluticasone propionate cream 0.05% applied twice daily, n=63 RCT 3 Fluticasone propionate ointment 0.005% applied twice daily, n=57 of 122 were children	Duration of treatment, 4 weeks (or less if eczema cleared sooner) Outcome Measures: RCT2 1) Global assessment, where success='cleared', 'excellent' or 'good'; and failure = 'fair', 'little' or 'worse' 2) Adverse events RCT 3 1) Global assessment, where success='cleared', 'excellent' or 'good'; and failure = 'fair', 'little' or 'worse' 2) Patients' self-assessment of success: success= totally, greatly, or moderately improved; failure = slightly improved, not changed, worsened or greatly worsened 3) Adverse events	1) 86% once daily vs. 891% twice daily success, difference 3% (95% CI -15.5 to 9.6), p = 0.644 2) 37% vs 35% reported adverse events 24% vs 17% were possibly related to treatment, predominantly signs or symptoms relating to skin or their eczema RCT 3 1) 77% once daily vs. 91% twice daily success, difference 13.5% (95% CI 0.6 to 26.4), p = 0.048 2) 72% vs. 91% success, difference 18.6% (95% CI 5.0 to 32.3), p=0.011 3) 49% vs 40% reported adverse events 8% vs 17% were possibly related to treatment, but no details of these adverse events were reported.	Funding of RCT3: not stated. Manufacturer (GlaxoSmithKline) assumed Refer to evidence tables for Richelli 1990[287] for details of RCT 1
Vernon HJ;Lane AT;Weston W; 1991 Apr [260]	Study Type: RCT Evidence level: 1+	48	Children with more than 15% of body surface area involving atopic eczema, and a score of at least 8/15 for severity* and an erythema score of at least 2. Age range: 6 months to	Intervention: Mometasone furoate 0.1% cream applied once daily (n=24) Comparison: Hydrocortisone 1.0% cream	Follow-up period: Up to 6 weeks treatment and follow-up; children whose condition had cleared by week 3, and those who had shown no improvement were withdrawn from the study.	1) 95% mometasone vs 75% HC, p=0.01 2) -40% vs -26%, p=0.03 3) No numerical data. No significant differences were found in mean values, nor in any change in mean cortisol	Funding: Schering-Plough Double-blind study. 30 children (15 in each group) completed the study early (median duration 3 weeks). Children who used antibiotics, antihistamines, or

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
			12 years	applied twice daily (n=24)	Outcome Measures: 1) Percentage improvement in severity* score from baseline 2) Change in % body surface area affected 3) Plasma cortisol levels 4) Adverse effects 5) Withdrawals	levels from baseline between groups. One child treated with HC had a plasma cortisol level of 5 microg/dl (below normal range, although this range was not quoted) on day 8 4) 8% (n=2) vs 0% stinging on application 0 vs 4% molluscum contagiosum on area treated 5) 63% vs 63% due to clearance of the condition 0 vs 13% lack of response 0 vs 4% (n=1) flare of asthma requiring systemic corticosteroids 0 vs 4% lost to follow-up 4% vs 0 S. aureus infection of scalp	emollients were removed from the study. Severity score: each of 5 signs/symptoms scored on a scale of 0-3 (none to severe). The quantities of TCS used were not stated.
Wolkerstorfer A;Strobos MA;Glazenburg EJ;Mulder PG;Oranje AP; 1998 Aug 261	Study Type: RCT Evidence level: 1+	22 Exclusions: use of systemic treatment for atopic eczema within 1 month	Children with moderately active atopic eczema. SCORAD scores 29 in the fluticasone group and 32 in the clobetasone group. Aged from 3-8 years, mean 4.9 years (fluticasone) and 4.1 years (clobetasone) Initial SCORAD: 29 (FP group); 32 (CB group) Medication (emollient, hydrocortisone acetate 1%, antihistamines) not	Intervention: Fluticasone propionate 0.05% cream applied once daily plus a vehicle cream once daily (n=12) Comparison: Clobetasone butyrate 0.05% cream applied twice daily (n=10; 9 completed treatment)	Follow-up period: 6 weeks; up to 4 weeks treatment, or less if SCORAD score below 9 ('clinically healed'), and 2 weeks follow-up after treatment completed. Outcome Measures: 1) SCORAD (mean score change from baseline to week 4) 2) SCORAD (mean score change from week 4 to week 6) 3) Urinary cortisol excretion (nmol/24 hours)	1) -19 (66%) vs -22 (69%), no statistically significant difference in groups 2) +13 (130%) vs +11 (110%) 3) No numerical data reported but it was noted that there were no significant differences between groups at baseline or weeks 4 or 6, p=0.8, and no signficant changes from baseline. In one child levels fell from 162.8 at baseline to 67 nmol/24hr at week 4, but returned to the pre-treatmnet level by week 6.	Funding: none declared. Basic skin care was used for all children. Double-blind One child in the clobetasone arm withdrew because of varicella. The quantities of TCS used were not stated.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
			used in the week before the trial started				
Wolkerstorfer A;Visser RL;De Waard van der Spek FB;Mulder PG;Oranje AP; 2000 Nov 328	Study Type: Cohort Non-randomised controlled trial Evidence level: 2-	31 children Group 1: 50% dilution of fluticasone propionate (FP) 0.05%, n=18 Group 2: a side-to-side 10%, 25% and 50% dilution of FP 0.05% for one week, then 10% dilution for one week, n=5 Group 3: 0% (emollient), 5%, 10% or 25% dilution of FP 0.05%, n=8	Children with severe refractory atopic eczema aged 5 months to 13 years, mean age not reported. SCORAD score >40 in 29 (94%)	Intervention: Group 1: 50% dilution of FP cream under wet wrap treatment for 2 weeks Group 2: different dilution (10%, 25% and 50%) of FP cream under wet wraps treatment for body symmetrically eczema for 2 weeks Group 3: different dilution (0% (emollient), 5%, 10% and 25%) of FP cream under wet wraps treatment for 2 children in each strength for 2 weeks Comparison: The serum corticol levels before and after wet wrap treatment in different dilution of FP strength groups	Follow-up period: Duration of treatment: 2 weeks Outcome Measures: 1) Mean serum cortisol levels (SD) a) Group 1 b) Group 2 c) Group 3 2) Adverse effects a) Group 1 b) Group 2 c) Group 3	1a) Overall, no significant decrease in cortisol levels at week 2, p=0.24. Levels were 'temporarily below the normal range' (0.2-0.8 micromol/l) in 3 (17%) children 1b) 0.45 (0.17) micromol/l at week 2 vs 0.42 (0.16) at baseline 1c) levels were below the normal range in 2/8 children (0.03 and 0.09 micromol/l). Serum cortisol levels vs FP quantity per body surface area (microgram per m2) for each of the 8 patients: 0.28 vs 0 0.46 vs 0 0.55 vs 564 0.39 vs 728 0.36 vs 835 0.09 vs 957 0.03 vs 1129 0.33 vs 2071 2a) 30% (6/18) upper respiratory tract infection 30% (6/18) folliculitis 5.5% (1/18) herpes simplex infection 5.5% (1/18) diarrhoea 5.5% (1/18) itching 2b) 40% (2/5) upper respiratory infection 40% (2/5) folliculitis	Funding: none declared. Tubifast was the bandage used. The cream was applied to the whole body. The bandage was rewetted every 2 hours with water using aspary bottle. Cortisol was measured at 9 o'clock in the morning in groups 1 and 2, at baseline and after 2 weeks. In group 3 serum cortisol and urinary timed morning cortisol/creatinine ratio was measured daily at 6 o'clock in the morning for the first week of treatment. SCORAD scores were also measured, but only selected numerical data were reported; results were mainly presented in graphs. The proportions with mild, moderate and severe atopic eczema were also reported, but the method of classification was not described.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						20% (1/5) abdominal pain 20% (1/5) itching 2c) 63% (5/8) folliculitis 12.5% (1/8) balanitis 12.5% (1/8) furunculosis	
Lucky AW;Grote GD;Williams JL;Tuley MR;Czernielewski JM;Dolak TM;Herndon JH;Baker MD; 1997 Mar 285	Study Type: RCT Evidence level: 3	20	Children with atopic eczema affecting more than 20% of body surface area, (mean 38%). Age range 11months to 11 years, mean 4.7 years desonide vs 2.6 years HC. Baseline cortisol levels 2-25 microg/ml	Intervention: Desonide ointment 0.05% applied twice daily (n=10) Comparison: HC ointment 2.5% applied twice daily (n=10)	Follow-up period: Duration of treatment: 4 weeks Outcome Measures: Change in cortisol levels in response to ACTH stimulation (measured at 30 minutes and 60 minutes after an intravenous dose)	% increase in stimulated 60 minute mean cortisol levels at day 28: 109% desonide vs 124% HC, p=0.69. No clinically or statistically significant differences reported between treatment for changes in ACTH Mean within-treatment change -0.4 microg/ml (-1.3%), p>0.8	Funding: none declared Mean quality of TCS applied was approximately 3g/day/child.
Patel L;Clayton PE;Addison GM;Price DA;David TJ; 1995 278	Study Type: Cross-sectional Evidence level: 3	28 Exclusions: children receiving inhaled or systemic corticosteroids in the preceding 6 months.	See intervention and comparisons	Intervention: Children aged 3.1-10.7 years, mean 7.2 years with atopic eczema affecting 16-90% (mean 58%) of body surface area and treated with HC ointment 1% since infancy for 3-10 years (mean 6.5 yrs) (n=14) Quantity used: 48.7-223.2 mg/square metre (median 134.2) body surface area/day for 3-10 years. 64% had used moderately potent	Follow-up period: N/A; cross-sectional study Outcome Measures: Plasma cortisol values (response to low-dose ACTH stimulation*); differences between medians in atopic eczema vs control groups, (95% CI)	Basal levels: 0.6 (95% CI -140 to 90 nmol/l) Peak: 0.2 (95% CI -125 to 50 nmol/l) Increment: p=0.8 (95% CI -120 to 95 nmol/l) Area-under-curve: 0.2 (95% CI -7725 to 1587, nmol/l) Time to peak: 0.02 (95% CI -10 to 0, min)	Funding: none declared *500ng/1.73 square metres body surface area

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
				TCS intermittently Comparison: Control group: children without atopic eczema being investigated for short stature, age 3.8-10.7 years, mean 7.8 years. Children had not received corticosteroids before the study, and had no endocrine abnormality or systemic disease (n=24)			
Lebwohl M; 1999 Aug 256	Study Type: RCT Evidence level: 1-	219	Children with moderate to severe atopic eczema who had failed to respond to at least 7 days consecutive treatment with a topical hydrocortisone preparation, the last application occurring within a week of enrolment in this study. Age 2-12 years	Intervention: Mometasone furoate cream 0.1% cream once daily (n=109) Comparison: Hydrocortisone valerate cream 0.2% twice daily (n=110)	Follow-up period: Duration of treatment, 3 weeks Outcome Measures: 1) Mean percentage improvement in disease severity. (Severity signs and symptoms assessed on a scale of 0-3 (none to severe: erythema, induration/lichenification, scaling/crusting, excudation, excoriation and pruritus. A target area of at least 20cm2 was selected for evaluation of treatment effect). 2) Physician's assessment of global clinical response vs baseline	1) Mometasone vs HC 87.2% vs 78.6% (p=0.01) 2) Global evaluation score at day 21 36.3 vs 19.6, p<0.01 3) 19.3% vs 17.3% reported adverse effects 3.7% vs 1.8% application-site reactions (other adverse effects 'not considered to be treatment-related' therefore no further details given) 4) Total withdrawals 19.6% Reasons: 16.5% vs 8% clearance of atopic eczema 2.7% vs 3.6% non-compliance	Funding: Schering Plough Inc Multicentre study (n=10). No other therapies for atopic eczema were permitted. Although described as a randomised controlled trial, no details of randomisation were given, nor any baseline data. Therefore it is not possible to know whether groups were similar other than in the intervention being given. Additionally, while treatment with a HC preparation had failed, it is assumed that this was a mild preparation, thereby not exposing the group receiving HC in this RCT to continued prior ineffective therapy. The physician's assessment of global clinical response compared to baseline at day 15 (p=0.009), day 22 (p=0.011), respectively. The quantities of TCS used were not stated.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
					3) Adverse effects 4) Withdrawals	0 vs 1% treatment failure 2% vs 5% lost contact	
Andersen BL;Andersen KE;Nielsen R;Stahl D;Niordson A;Roders GA; 1988 268	Study Type: RCT Within patient left-right side comparison Evidence level: 1-	96 Exclusions: primary bacterial or viral skin lesions; secondarily infected lesions, treatment with systemic corticosteroids or potent TCS within 2 weeks	Children with dry bilateral symmetrical atopic eczema Age range 2 months to 13 years, mean 4.9 years	Intervention: Hydrocortisone 1% lipocream (Mildison) applied twice daily Comparison: Hydrocortisone 1% ointment (Uniderm) applied twice daily	Follow-up period: Duration of treatment, 4 weeks Outcome Measures: 1) Change in global severity* of atopic eczema 2) Global improvement in skin lesions (% in each category): a) clearance b) considerable improvement c) definite improvement d) minimal improvement e) no change f) worse 3) Patients' preference (based on cosmetic acceptability) 4) Adverse effects	1) -1.0 (59%) HC lipocream vs -0.9 (53%) HC ointment 2a) 37% vs 33% 2b) 11% vs 15% 2c) 26% vs 24% 2d) 16% vs 14% 2e) 4% vs 8% 2f) 5% vs 7% p>0.05 between groups 3) 73% preferred lipocream vs 18% ointment, p<0.001 4) 0 vs 1% (n=1) pustules on target area	Funding: none declared *Severity measured on a 5-point scale (0-4, none to severe) One child from the hydrocortisone 1% ointment group was excluded from the analysis because of non-compliance It is reported that analysis of baseline data was undertaken, but no baseline/demographic data were shown.
Olholm LP;Brandrup F;Roders GA; 1988 269	Study Type: RCT Evidence level: 1-	60 Exclusions: primary bacterial or viral skin lesions; secondarily infected lesions; needing treatment with systemic	Children with dry bilateral symmetrical atopic eczema; 51 children were aged under 10 years, but the mean age was not reported	Intervention: Hydrocortisone 1% oil-in-water emulsion (Lipocream) applied twice daily Comparison: Hydrocortisone 1% ointment (Uniderm) applied twice daily	Follow-up period: Duration of treatment, 4 weeks Outcome Measures: 1) Global severity* of atopic eczema (% with none, slight, moderate, severe, very severe at endpoint) 2) Global improvement in skin disease	1) 41% lipocream vs 38% ointment none 43% vs 45% slight 12% vs 14% moderate 3% vs 3% severe No statistical analysis 2) 2% vs 2% worse 2% vs 2% no change 7% vs 5% minimal	Funding: none declared *Severity measured on a 5-point rating scale (0-4, none to very severe) No baseline data were given (other than severity scores). Two children withdrew from the study, and data were not included for some children for the outcomes cosmetic acceptability (n=1) and global improvement (n=3).

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
		corticosteroids; use of potent corticosteroids within two weeks			3) Patients' preference (in relation to cosmetic acceptability)	improvement 29% vs 33% definite improvement 20% vs 20% considerable improvement 40% vs 38% clearance No statistical analysis 3) 26% preferred lipocream 25% found the lipocream was worse 49% no difference between products	
Veien NK;Hattel T;Justesen O;Norholm A;Verjans HL; 1984 [258]	Study Type: RCT Within-patient left-right side comparison Evidence level: 1+	40	Children with chronic symmetrical, bilateral atopic eczema. Mean severity score 2.6 (scale 0-4). Age 10 months to 10 years, mean 4.1 years	Intervention: Hydrocortisone 17-butyrate 0.1% cream (Locoid), applied twice daily Comparison: Hydrocortisone cream 1% (Uniderm), applied twice daily	Follow-up period: Duration of treatment, 4 weeks (or until complete clearance of lesions of the side involved, whichever was shorter) Outcome Measures: 1) Global severity of atopic eczema (mean reduction in scores, on 5-point rating scale where 0=none, 1=slight, 2=moderate, 3=severe, 4=very severe) 2) Clearance rate 3) Investigator and patients/parents preference for HC-17-butyrate 0.1%, where moderate, good or excellent associated with score reductions of at least 1, 2, and 3 points on the rating scale.	1) HC-17-butyrate 0.1% vs HC 1%: -2 (77%) vs -1.6 (62%), p<0.05 2) 60% vs 30%, p<0.01 3) Reported to be significantly in favour of HC-17-butyrate 0.1%; investigator's preference p<0.01, patients/parents preference p<0.01 4) 'No serious adverse events'	Funding: none declared The quantities of TCS used were not stated.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
					4) Adverse events		
Veien NK;Hattel T;Justesen O;Norholm A;Verjans HL; 1984 258	Study Type: RCT Within-patient left-right side comparison Evidence level: 1+	40	Children with chronic symmetrical, bilateral atopic eczema. Mean severity score 2.6 (scale 0-4). Age 10 months to 10 years, mean 4.1 years	Intervention: Hydrocortisone 17-butyrate 0.1% cream (Locoid), applied twice daily Comparison: Hydrocortisone cream 1% (Uniderm), applied twice daily	Follow-up period: Duration of treatment, 4 weeks (or until complete clearance of lesions of the side involved, whichever was shorter) Outcome Measures: 1) Global severity of atopic eczema (mean reduction in scores, on 5-point rating scale where 0=none, 1=slight, 2=moderate, 3=severe, 4=very severe) 2) Clearance rate 3) Investigator and patients/parents preference for HC-17-butyrate 0.1%, where moderate, good or excellent associated with score reductions of at least 1, 2, and 3 points on the rating scale. 4) Adverse events	1) HC-17-butyrate 0.1% vs HC 1%: -2 (77%) vs -1.6 (62%), p<0.05 2) 60% vs 30%, p<0.01 3) Reported to be significantly in favour of HC-17-butyrate 0.1%; investigator's preference p<0.01, patients/parents preference p<0.01 4) 'No serious adverse events'	Funding: none declared The quantities of TCS used were not stated.
Munkvad M; 1989 Dec 264	Study Type: RCT Within-patient left-right side comparison Evidence level: 1-	30	Children with mild to moderate bilateral symmetrical atopic eczema Mean age 11.8 years (range not reported)	Intervention: Clinitar (extract of crude coal tar) cream applied twice daily Comparison: Hydrocortisone 1% cream applied twice daily	Follow-up period: Duration of treatment, up to 4 weeks Outcome Measures: 1) Change in severity* scores of atopic eczema from baseline a) infiltration b) erythema c) lichenification d) scratch marks	1a) -0.97 (75%) vs -0.97 (76%) 1b) -0.8 (71%) vs -0.87 (74%) 1c) -1.0 (70%) vs -1.13 (79%) 1d) -0.54 (70%) vs -0.6 (78%) 1e) -1.07 (78%) vs -1.0 (75%) 'no significant differences between treatment'; p value	Funding: Pharma medica a-s supplied the trials material. Smith & Nephew assisted in preparing the paper No other medicines were permitted during the study period Severity score used for infiltration, erythema, lichenification, excoriation and dryness, measured on a 5-point scale: 0-4 (none to severe) No baseline/demographic data (other than severity scores) were reported for the two groups.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
					e) dryness	not reported	
					2) Adverse effects	2) Reported in 6 children ('itching and soreness'); 5 in the coal tar group and 1 in the HC group.	
Smitt JHS;Winterberg DH;Oosting J; 1993 257	Study Type: RCT Evidence level: 1+	40	Children with atopic eczema, with a mean severity score of at least 4*, with at least two symptoms rated as moderate. Eczema affected 44% of mean body surface area of the triamcinolone group and 53% of the alclometasone group Age 1-15 years Mean age, 5.1 years in the triamcinolone acetonide arm, and 3 years in the alclometasone diproprionate arm, p=0.046	Intervention: Triamcinolone acetonide cream 0.1% applied twice daily (n=20) Comparison: Alclometasone diproprionate cream 0.05% applied twice daily (n=20)	Follow-up period: Duration of treatment, 3 weeks Outcome Measures: 1) Severity of signs and symptoms, mean change from baseline to end of week 2 for: a) erythema b) lichenification c) pruritus d) exudation (*4 point scale: 0=absent, 1=mild, 2=moderate, and 3=severe) 2) Serum cortisol levels (fasting, taken at 8.30am)	1a) 1.9 (-75%) triamcinolone vs 1.4 (-53%) alclometasone, p=0.047 1b) 1.6 (-65%) vs 0.6 (-25%), p=0.004 1c) 2.1 (-72%) vs 1.4 (-48%), p=0.005 1d) 1.7 (-94%) vs 0.7 (-45%), p=0.009 2) Results for 23 patients presented in the report, but no units nor normal ranges to know whether the levels were high, low, or normal. It was also reported that there were 'no significant differences between groups', meaning that there were no significant changes from baseline to weeks 2 or 3.	Funding: Essex (Nederland) BV, subsidiary of Schering Plough Corporation USA. Use of bath oils, white petrolatum and antihistamines was continued for as long as necessary. Baseline mean values for each parameter calculated from data reported in the paper - mean change was reported, but this did not clearly state that the changes were reductions. The quantities of TCS used were not stated.
Chunharas A;Wisuthsarewong W;Wananukul S;Viravan S; 2002 Apr 342	Study Type: Cohort Evidence level: 2+	50 (48 analysed) Mometasone furoate 0.1% cream plus loratadine syrup, n=24 Mometasone furoate 0.1% cream plus placebo	Children with atopic eczema who an affected are at least 4cm2, and severity scores (SCORAD) of at least 10 out of 18 (mean was 12); pruritus of the target area present, with a minimum score of 2.5 (scale 0-3), mean was ~2.7 Age 2-11.2 years, mean 6.2 years	Intervention: Loratadine syrup once daily (5ml if weight up to 30kg, 10mls if over 30kg) in addition to mometasone furoate 0.1% cream, applied once daily after a bath in the evening Comparison:	Follow-up period: Duration of treatment, 15 days Outcome Measures: 1. Severity of the disease (% change in SCORAD score from baseline) 2. Physician global assessment	1. -84% loratadine vs -85% placebo, p=0.883 (actual score change 12.4 to 1.94 vs 12.21 to 1.83) 2. 75% vs 91.6% had 75-100% improvement, p=0.245 8.3% vs 8.3% had 50-75% improvement, p=1.0 17% vs 0% had <50% improvement, p=0.109	Funding: none declared. The study is described as a double-blinding, multicentre trial, however, the methods of blinding are unclear. Two children from the loratadine group withdrew (1 due to impetigo, 1 because rash 'very much improved') Although the volume (and not strength) was reported in the paper, it is assumed that the only available

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
		syrup, n=24	Exclusions: history of hypersensitivity to either drug, or nonresponsvie to mometasone before the study. If antibiotics or antihistamine were used or severe illness and side effects were noted, the patient was withdrawn from the study.	Placebo syrup once daily (5ml if weight up to 30kg, 10mls if over 30kg) in addition to mometasone furoate 0.1% cream, applied once daily after a bath in the evening	Cleared=100% improvement Marked=75-100% improvement Moderate=50-75% improvement Slight=<50% improvement No change Exacerbation 3. Pruritus score (0= none to 3=severe; % change from baseline) 4. Adverse effects	3. -90% vs -97% (from 2.77 to 0.29 vs 2.63 to 0.09), p=0.097 4. No reports of drowsiness or difficulty awakening 1 child in each group reported dizziness 1 vs 0 nausea 0 vs 1 anorexia	proprietary preparation of loratadine was used (5mg/5ml).
Kirkup ME;Birchall NM;Weinberg EG;Helm K;Kennedy CT; 2003 Sep 255	Study Type: RCT Evidence level: 1+	Two multicentre RCTs in one report Exclusions: signs of skin infection; severe atopic eczema requiring hospital admission; treatment with very potent or systemic corticosteroids in the previous 3 weeks; history of adverse response to corticosteroids	Children experiencing a flare of moderate to severe atopic eczema (total atopic eczema score of 6 or more*), treated at outpatient clinics. Age 2-14 years, mean age 8 years Mean number of body areas affected, 67% (8 out of a possible 12)	Intervention: Study A: Fluticasone propionate 0.05% cream (n=70) Study B: Fluticasone propionate 0.05% cream (n=66) Acute phase - twice daily for 2-4 weeks until atopic eczema stabilised Maintenance phase - intermittently up to twice daily as required for 12 weeks plus emollients as required Comparison: Study A: Hydrocortisone cream 1% (n=67)	Follow-up period: Duration of treatment, acute phase (2-4 weeks) and maintenance phase (up to 12 weeks) Outcome Measures: Study A 1) Total atopic eczema score* (reduction in scores, and mean difference between groups) 2) Patient's diary at end of acute phase (change in score vs baseline; difference in scores at endpoint. Score used was 1-7, worse than ever to better than ever) a) rash b) itch c) sleep disturbance	Study A (fluticasone vs HC 1%) 1a) At the end of the acute phase: -4.91 (41%) vs -2.37 (20%), difference -2.39, 95% CI -3.47 to -1.31, p<0.001 1b) At the end of the maintenance phase: -6.87 (57%) vs -4.84 (41%), difference -1.88, 95% CI -3.20 to -0.56 p=0.006 2a) +31% vs +8%, difference 0.81, 95% CI 0.45 to 1.16, p<0.001 2b) +29% vs +9%, difference 0.70, 95% CI 0.33 to 1.07, p<0.001 2c) +26% vs +12%, difference 0.46, 95% CI 0.08 to 0.84, p=0.019	Funding: Glaxo Wellcome R&D UK. Multicentre RCT. The two studies were identical in design. *Total atopic eczema score (Max, 21) = Number of body areas affected (out of possible 12 body areas) + sum of three signs (erythema, excoriation and lichenification) graded as 0-3 for target area (max 9) Recurrence of atopic eczema was defined as an increase of 1.0 in either the number of body areas affected or in the sum of scores for the target area. Use of regular inhaled or intranasal corticosteroids was permitted

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
				Study B: Hydrocortisone 17-butyrate cream 0.1% (n=62) Acute phase - twice daily for 2-4 weeks until atopic eczema stabilised Maintenance phase - intermittently up to twice daily as required for 12 weeks plus emollients as required	3) Physician's assessments: Improved=better than ever, or better than usual, Not improved= same, worse than ever, or worse than usual 4) Median time to recurrence during the maintenance phase (days) 5) Adverse effects 6) Withdrawals 7) Quantity of TCS used Study B 1) Total atopic eczema score* (reduction in scores, and mean difference between groups) 2) Patient's diary at end of acute phase (change in score vs baseline; difference in scores at endpoint. Score used was 1-7, worse than ever to better than ever) a) rash b) itch c) sleep disturbance 3) Physici	3) 94% vs 85% improved, p=NS 4) 62 (range 7-118) vs 36 (7-114) 5) 29% vs 31% reported an adverse event 7% vs 10% general symptoms 8.5% vs 6% influenza 8.5% vs 8.5% 'miscellaneous events related to the skin' Possibly related to treatment: 1% vs 0% folliculitis and ringworm 0 vs 1% severe flare with secondary infection 6) 26% vs 20% reasons: 2.9% vs 12% treatment failure 10% vs 3% non-compliance/personal 4.2% vs 1.5% early cure 0% vs 1.5% adverse event 11.4% vs 3% protocol violation/no reason 7) median 57g (range 10-259) vs 60g (15-252) Study B (fluticasone vs HC-17-butyrate 0.1%) 1a) At the end of the acute phase: -4.37 (41%) vs -4.52 (37%) difference -1.25, 95% CI -2.46 to -0.05, p=0.042	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						1b) At the end of the maintenance phase: -6.76 (63%) vs -6.78 (56%) difference -1.39, 95% CI -2.72 to -0.05 p=0.042 2a) +11% vs +10%, difference 0.38 95% CI -0.01 to 0.77, p=0.056 2b) +11% vs +12%, difference 0.50 95% CI 0.09 to 0.92 p=0.017 2c) +7% vs +7%, difference 0.48 95% CI 0.11 to 0.85, p=0.011 3) 98% vs 84% improved, p=0.024 4) 51 (range 7-121) vs 57 (9-123) 5) 42% vs 35% reported an adverse event 12% vs 8% upper respiratory tract infection 11% vs 2% cough 8% vs 15% 'miscellaneous events related to the skin' Possibly related to treatment: 1.5% (n=1) vs 0% red papules/boil 0 vs 3.2% (n=2) itchy skin after applying cream 0 vs 1.6% minor skin infections and pustules 0 vs 1.6% impetigo on the face	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						6) 11% vs 18% reasons: 0% vs 8% treatment failure 3% vs 4.8% non-compliance/personal 1.5% vs 4.8% adverse event 6% vs 9.7% protocol violation/no reason 7) Median 62g (17-201) vs 59g (16-126)	
Sefton J;Galen WK;Nesbitt LT;Landow RK; 1983 283	Study Type: RCT Evidence level: 1-	66	Children/ young people with atopic eczema, bilaterally symmetrical lesions in a chronic stable state. Age 4 months to 22.8 years (mean 5.3 years). [EL=1-] only completers analysed (n=54, 82%). Reasons for withdrawal: 10 lost to follow-up, 2 intercurrent medical conditions	Intervention: Triamcinolone acetonide cream 0.1% applied twice daily (n=66) Comparison: HC valerate cream 0.2% applied twice daily (n=66)	Follow-up period: Duration of treatment, 2 weeks Outcome Measures: 1) Severity 2) Global evaluation 3) Adverse effects	1) No numerical data. Results shown in graphs only 2) 74% vs 74% experienced 'clearance' or an 'excellent response' 3) 3% triamcinolone vs 3% HC transient stinging on application	Funding: none declared Double-blind
Ellison JA, Patel L et al 2000 279	Study Type: Cross-sectional Evidence level: 3	46	See interventions and comparisons	Intervention: Children/adolescents with atopic eczem, attending a tertiary referral clinic. Age 0.7-18.7 years, median 9.3 years. Had been using TCS, applied twice daily since infancy, median 6.9 years (0.5-17.7) (n=35) 7 had used HC 1%	Follow-up period: N/A Outcome Measures: 1) Serum cortisol levels in response to low-dose ACTH*; differences between children with atopic eczema and controls 2) Correlation between plasma cortisol response to the test and severity of atopic eczema and its treatment (variables	1) No significant differences in basal, peak, incremanet, or time to peak cortisol values between children treated with mild or moderately potent TCS and controls. All children treated with potent TCS failed the ACTH test. Peak, increment and area-under-curve cortisol responses were significantly lower in the atopic eczema group, with no significant difference between groups in baseline or time to	Funding: none declared *500ng/1.73 square metre body surface area, after discontinuing TCS treatment for 24 hours (normal response: peak plasma cortisol 500nmol/l or more, increment 200nmol/l or more) Subggroup analysis of 7 children with severe eczema ws also reported, although this was confounded by other treatments (inhaled and/or systemic corticosteroids).

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
				17 used moderately potent TCS 4 used potent TCS Comparison: Children being investigated for short stature, age 3.8-17.3 years, median 10.3 years. Never treated with corticosteroids (n=14)	considered by multiple linear regression; treatment and severity scores, age, prepubertal status, treatment duration)	peak cortisol values. 3) Severity score was the only significant variable influencing peak (r2=24%, p=0.0016) and increment (r2=25%, p=0.014) cortisol response.	
Stalder JF;Fleury M;Sourisse M;Rostin M;Pheline F;Litoux P; 1994 Oct 270	Study Type: RCT Evidence level: 1+	40 n=19 desonide applied once daily n=21 vehicle applied once daily	Children aged 4.5 months - 15 years (mean 40 months) with atopic eczema. Exclusions: clinical infection requiring antibiotic therapy	Intervention: Desonide Comparison: Vehicle	Follow-up period: 7 days Outcome Measures: 1) Change in clinical score	1) 66.7% vs 15.8% showed 'improvement or resolution), p<0.001	This was a DB RCT. All other treatments for atopic eczema were excluded during the study. The effects of treatment on Staph aureus denisty was also reported - data not reproduced here.
Prado de Oliveira ZN;Cuce LC;Arnone M; 2002 284	Study Type: RCT Evidence level: 3	25	Children with atopic eczema, with minimum total severity score* of 8 (and 2 for erythema) Age range 2-12 years, mean 7.2 years mometasone vs 4.8 years desonide	Intervention: Mometasone furoate 0.1% once daily (n=13) Comparison: Desonide 0.05% once daily (n=12)	Follow-up period: Duration of treatment: 42 days Outcome Measures: 1) Atrophy (on scale of 0-3, absent to intense) 2) Other adverse effects	1) 'evidence of atrophy' in 17% desonide vs 31% mometasone (mean scores between 0.2 and 0.4 according to graph) 2) n=1 vs 0 pneumonia 1 vs 3 ardor (burning) 0 vs 1 appearance of laguna (fine hair)	Funding: none declared *Severity of erythema, lichenification, desquamation, excoriation, pruritus on a scale of 0-3 (none to severe). Use of emollients was permitted. Severity and global improvement were also evaluated but data not reproduced here. Atrophy was assessed by measuring the following signs on a four-point scale (thinning of the skin, striae, shiny skin, telangectasia, loss of elasticity, loss of normal lines on the cutaneous surface).
Rafanelli Aea;	Study Type:	60	Children with atopic	Intervention:	Follow-up period:	1) -6.7 (85%) vs -4.8 (66%),	Funding: none declared

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
1993 259	RCT Evidence level: 1+		eczema, showing three signs/symptoms (erythema, induration, pruritus)in the area to be observed durig the study. Total severity score at entry at least 6; each sign/symptom scored on a scale of 0-3 (none to severe) Mean age about 7 years. Duration of disease significantly longer in the mometasone group (26.7 vs 16.4 with clobetasone), p<0.05.	Mometasone furoate 0.1% applied once daily (n=30) Comparison: Clobetasone 0.05% applied twice daily (n=30)	Duration of treatment, up to 3 weeks. Outcome Measures: 1) Reduction in mean disease severity score from baseline 2) Response to treatment a) cleared (100% improvement) b) marked improvement (>75%) c) moderate improvement (50-75%) d) slight improvement (<50%) e) no change 3) Adverse events	p<0.01 2a) 50% vs 6.7% 2b) 30% vs 36.6% 2c) 20% vs 50% 2d) 0 vs 6.7% 3) No 'drug-induced' skin alterations nor atrophy. No adverse events were reported	The quantities of TCS used were not stated.
Lassus A; 1984 Oct 263	Study Type: RCT Evidence level: 1-	43	Children aged 5-11 years with atopic eczema, stable or worsening for more than 1 week. Three signs/symptoms of eczema (erythema, induration, pruritus) with a total severity score* of 6 or more (baseline score was about 8)	Intervention: Alclometasone dipropionate cream 0.05% applied twice daily (n=22) Comparison: Clobetasone butyrate cream 0.05% applied twice daily (n=21)	Follow-up period: Duration of treatment, 2 weeks Outcome Measures: 1) Severity score (mean change from baseline) 2) Investigator's global evaluation a) no. children with at least 75% improvement b) no. children with 100% improvement 3) Adverse effects	1) -7.0 (85%) vs -7.14 (86%), p >0.10 2a) 64% vs 75% 2b) 41% vs 48% 3) 10% (n=2) vs 0 stinging	Funding: none declared Double-blind study *Severity score used: 0=absent, 1=mild, 2=moderate, 3=severe Lesions on the face, neck, trunk, and upper and lower extremities were included as study areas It was not stated whether an emollient was also used. The quantities of TCS used were not stated.
Lassus A; 1983	Study Type: RCT Evidence level: 1+	40	Children with atopic eczema, stable or worsening for more than 1 week. Three signs or symptoms (erythema, induration, pruritus) with	Intervention: Alclometasone dipropionate cream 0.05%, applied twice daily (n=20)	Follow-up period: Duration of treatment, 2 weeks Outcome Measures: 1)	1) -5.85 (76%) vs-5.55 (69%), p>0.10 2a) 10% vs 15%	Funding: none declared Double-blind study.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
[262]			a severity score* of 6 or more (score 7.70 and 8.05 in alclometasone and HC groups respectively) Age 5-11 years, mean about 8 years.	Comparison: Hydrocortisone butyrate cream 0.1%, applied twice daily (n=20)	Severity score (mean change from baseline) 2) Investigator's rating of improvement a) 100% b) >75% c) 51-75% d) 26-50% e) 1-25% f) 0 3) Adverse effects	2b) 30% vs 20% 2c) 55% vs 45% 2d) 5% vs 15% 2e) 0 vs 0 2f) 0 vs 5% 3) 10% vs 5% stinging	*Severity score used: 0=absent, 1=mild, 2=moderate, 3=severe. Areas treated were the face, neck, trunk, and upper and lower extremities. The quantities of TCS used were not stated.
Bleehen SS;Chu AC;Hamann I;Holden C;Hunter JA;Marks R; 1995 Oct [286]	Study Type: RCT Evidence level:			Intervention: Comparison:	Follow-up period: Outcome Measures:	1)	
Richelli C;Piacentini GL;Sette L;Bonizzato MC;Andreoli A;Boner AL; 1990 [287]	Study Type: RCT Evidence level: 1-	30 Once daily, n=9 Twice daily at 8am and 3pm, n=13 Twice daily at 3pm and 8pm, n=8	Children with atopic eczema who had not used TCS within 2 weeks. Mean age ranged from 4-5.5 years across groups.	Intervention: Clobetasone 17-butyrate 0.05% lotion applied once daily Comparison: Clobetasone 17-butyrate 0.05% lotion applied twice daily (at 8am and 3pm) Clobetasone 17-butyrate 0.05% lotion applied twice daily (at 3pm and 8pm)	Follow-up period: Duration of treatment, 1 week Outcome Measures: 1) Severity of signs and symptoms 2) Serum cortisol and ACTH levels	No numerical data for 1) or 2). Data shown in graphs only, showing reduction in severity of signs and symptoms in all groups. It was reported that there were 'no differences' between groups.	Funding: none declared

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
Devillers ACA;de Waard-van der Spek FB;Mulder PGH;Oranje AP; 2002 [329]	EI=3	Intervention: Application of fluticasone propionate (FP) 0.05% wet wraps once daily to whole body for one week. Thereafter, application of FP to affected areas, and emollient to unaffected areas for days 1-4 of the week, followed by emollient only for days 5-7 of the week. Wet wrap dressings worn for a minimum of 12 hours per day. 5% dilution was used on the face A side-to-side left-right treatment comparison was made using 5% and 10% dilutions. Comparison: N/A	14 children and 12 adults	Adults and children with refractory atopic eczema who visited paediatric outpatient department between March 1999 and 2000, unsuccessfully treated with topical corticosteroids and emollients. Age range of children 6 months to 10 years, mean 3 years. Mean SCORAD score in children 39.09.	1) SCORAD (mean change form baseline to day 9) 2) Serum cortisol levels (nmol/ml), at day 7	1) -28 (71%), 95% CI 20.87 to 34.40, p<0.0005 2) No values <200nmol/ml (although temporary drop to <200ml seen in 3 children mid week). Baseline minimum 28, maximum 890, median 585; Day 7 minimum 206, maximum 549, median 410, p<0.016	Funding: none declared Serum cortisol measured at 6 a.m.; reference value for lower limit 200 nmol/l. One child did not use/need a facial mask. Three used an additional mild to moderate topical corticosteroids to treat facial or scalp lesions.
McGowan R;Tucker P;Joseph D;Wallace AM;Hughes I;Burrows NP;Ahmed SF; 2003 Sep [331]	EI=3	Intervention: Wet wrap dressings with emollient (n=1) or beclomethasone dipropionate, strength not stated, diluted to 10% (n=6) or 25% (n=1) applied under tubular bandages. Bandages left on for 24 hours a day for up to 2 weeks, reducing to overnight use for 1 week, then as required for the remaining 12 week	8	Children with atopic eczema aged 3.3-8.8 years, median 5.1 years	1) Lower leg length velocity (knemometry); millimetres per week 2) Urinary deoxypyridinoline crosslink excretion (UDPD); median rate, nmol/l	1) 0.42 (vs 0.43 during the pretreatment period), p value not reported 2) 26.3 (vs 25.9 in pretreatment period), p value not reported	Funding: Addenbrookes Charities Committee, the Marmaduke Shiled Fund, Serono Pharmaceuticals Ltd, and Mason Medical Research Foundation.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
		Comparison: N/A					
Boner AL;Richelli C;De SG;Valletta EA;Ferrari S;Mengoni M; 1985 Feb [274]	EI=3	Intervention: Clobetasone butyrate cream 0.05% applied twice daily for 7 days (n=17) Comparison: Clobetasone butyrate cream 0.05% applied twice daily for 14 days (n=12)	29 Exclusions: children treated with topical corticosteroids within 2 weeks	Children with chronic atopic eczema Mean age 5 years and 7 months in the one-week arm and 1 year 8 months in the two-week arm	1) Plasma cortisol concentrations (micromol/l; before vs after) 2) ACTH concentrations (pg/ml; before vs after)	1a) Group receiving 7 days' treatment At 0800hrs: 0.4 vs 0.4, p<0.5 At 2000hrs: 0.29 vs 0.30, p<0.5 Group receiving 14 days' treatment At 0800hrs: 0.44 vs 0.39, p<0.3 At 2000hrs: 0.27 vs 0.28, p<0.3 2) Group receiving 7 days' treatment At 0800hrs: 41 vs 36, p<0.3 At 2000hrs: 38 vs 34, p<0.4 Group receiving 14 days' treatment At 0800hrs: 31 vs 37, p<0.5 At 2000hrs: 31 vs 34, p<0.3	Funding: none declared Children were reported to have been randomised to one or two weeks treatment; but for the outcome measured, the evidence level is considered to be a before and after study [EL=3]
Furue M;Terao H;Rikihisa W;Urabe K;Kinukawa N;Nose Y;Koga T; 2003 Jan [280]	EI=3	Intervention: Adverse effects to TCS Comparison: N/A	666	1271 people with atopic eczema who had been followed fro 6 months in Japanese outpatient clinics (666 [52%] infants or children; up to 12 years). All were treated with TCS and emollients. Infants' mean age	1) Cumulative incidence of adverse effects (infants vs children) 2) Effects of TCS (and other variables) on three major adverse effects, analysed using stepwise logistic regression analysis a) telangiectasia on cheek	1) 0.5% vs 1% hyperspertirchosis 0 vs 2.3% telangiectasia on cheek 1.5 vs 5.2% skin atrophy of antecubital fossae 1.9% vs 4.1% skin atrophy of popliteal fossae 0 vs 0 striae atrophica 0 vs 1.3% acne and folliculitis 1.4% vs 2.1% bacterial	Funding: Japanese Ministry of Education, Culture, Sports, Science and Technology. TCS were classified as 'strongest, very strong, strong, mild, weak'. It is unknown which products the classification relates to. Quantity of TCS used (median, infants and children) face 1g vs 15g scalp 0 vs 0 trunk 21g vs 45g

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
				1.1 year, children mean 5.6 years	b) skin atrophy of antecubital fossae c) skin atrophy of popliteal fossae	infection 1.9% vs 0.6% fungal infection 0 vs 0.4% steroid-induced dermatitis 0 vs 0.4% contact dermatitis 2a) duration: OR 1.77 (95% CI 1.41 to 2.22) p=0.0000 age: OR 3.61 (1.84 to 7.1), p=0.000 duration 6 years: OR 0.534 (0.396 to 0.72), p=0.000 doses of TCS to face (20g 'changing point'): OR 1.37 (1.14 to 1.65), p=0.0013 2b) age: OR 2.8 (95% CI 1.75 to 4.47) p=0.0000 duration: OR 1.24 (1.12 to 1.38), p=0.000 duration 9 years: OR 0.626 (0.464 to 0.845), p=0.0022 doses of TCS to truck and extremities (500g 'changing-point'): OR 3.82 (1.07 to 13.6), p=0.0465 2c) duration: OR 1.35 (95% CI 1.19 to 1.52) p=0.0000 age: OR 2.08 (1.21 to 3.56), p=0.0063 duration 9 years ('changing point'): OR 0.492 (0.345 to 0.7), p=0.0001	extremities 25g vs 45g Type used (n, infants vs children) Face: strongest 0 vs 0 very strong 1 vs 5 strong 1 vs 17 mild 94 vs 71 weak 4 vs 7 Scalp: strongest 0 vs 0 very strong 1 vs 5 strong 1 vs 17 mild 94 vs 71 weak 4 vs 7 Trunk and extremities strongest 1 vs 1 very strong 17 vs 27 strong 34 vs 37 mild 46 vs 35 weak 2 vs 0 'changing point' believed to be threshold at which comparison was made
Queille C;Pommarede R;Saurat JH; 1984 Jan [277]	EL=3	Intervention: A topical corticosteroid preparation, applied once daily. One of: betamethasone dipropionate (n=5), difluorocortolone	26	Children with severe atopic eczema requiring hospitalisation. Children had not been treated with TCS for at least 2	Plasma cortisol levels (mean, microg/100ml, before vs after treatment)	Betamethasone dipropionate 10.46 vs 4.14 (-61%) Difluorocortolone valerianate 12.35 vs 3.4 (-72%)	Funding: none declared No statistical analysis. No normal range given for serum cortisol, and no analysis vs baseline

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
		valerianate (n=4), halcinonide (n=4), clobetasone butyrate (n=5), desonide (n=5), fluocortine butylester (n=3 Comparison: N/A		weeks, and never with systemic corticosteroids. Mean cortisol levels at baseline 10.96 (SD 3.46 microg/100ml). Age 5 months to 12 years.		Halcinonide 12.53 vs 7.76 (-38%) Clobetasone butyrate 12.22 vs 9.67 (-21%) Desonide 9.53 vs 9.67 (+1%) Fluocortine butylester 8.2 vs 9.43 (+15%)	Quantity of TCS used (g/day/square metre): 5.9 betamethasone 9 difluorocortolone 3.98 halcinonide 5.3 clobetasone 9.9 desonide 13 fluocortine
Friedlander SF;Hebert AA;Allen DB;Fluticasone Pediatrics Safety Study Group.; 2002 Mar [276]	EL=3	Intervention: Fluticasone propionate cream 0.05% applied twice daily to all lesions, including facial areas but not nappy areas, eyelids, perioral area, nostrils, or areas of atrophy Comparison: N/A	51 Exclusions: acute self limiting eczema; use or anticipated use of topical or inhaled corticosteroids within 1 week, or continuous therapies including ciclosporin, ultraviolet light and topical products within 4 weeks	Children with moderate to severe atopic eczema affecting more than 35% of the body surface area (mean body surface area 64%). Age range 3 months to 5 years (63% aged 3 months to 2 years, and 37% aged 3 to 5 years)	1) Serum cortisol levels in response to stimulation with cosyntropin (mean difference in pre- and post-stimulation values) 2) Adverse events	1) Prestimulation -1.78 microg/dl, p=0.1734 Poststimulation -2.49 microg/dl, p=0.719 Two children (4.7%, 2/43) had serum cortisol values below 18 microg/dl following stimulation at treatment end. They had been treated for 4 and 5 weeks. 2) 50% reported 39 adverse events, 'most frequently' fever and cold symptoms. Drug-related adverse events: 1 burning 1 urticaria 1 erythematous rash 3 telangiectasia	Funding: Glaxo Wellcome Inc 17% withdrew from the study (10% in older group, 7% in younger group) 'normal adrenal response' defined as a poststimulation cortisol peak value of more than 18.0 microg/dl measured by fluorescence-polarisation immunoassay
Boner AL;Richelli C;De SG;Antolini I;Aprili F;Mengoni M;	EL=3	Intervention: Clobetasone butyrate cream 0.05% applied three time a day for 1 week, then twice daily for 3 weeks	12 Exclusions: children receiving oral corticosteroids during the study period or in the	Children with chronic atopic eczema, with pruritus, persistent scratching, excoriations, crusting and	Cortisol level measured following administration of tetracosactrin at 8a.m. (dose given: 0.25mg/square metre by intramuscular injection)	At 0800hrs: 12.8 vs 15.5 microg/ml At 0830hrs: 32.4 vs 28.7 microg/ml At 0900hrs: 42.3 vs 37.5 microg/ml	Funding: none declared. Mean quantity of clobetasone used during the study period was 82.5g The significance of any changes in cortisol

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Reviewer comment
1985 [275]		Comparison: N/A	previous 3 months	thickening or lichenification Age range 2-13 years, mean 8.2 years	Mean levels before vs after	At 1800hrs: 12.7 vs 10.9 microg/ml p>0.1 for all comparisons	levels in individual children was not considered in the trial report
Hebert AA; 2006 Sep [543]	Study Type: Other Open-label study with no comparator group Evidence Level: 3	Intervention: 0.05% Fluticasone propionate lotion Comparison: Serum cortisol levels measured before and after treatment	n=44	Children aged 3 months to 6 years with moderate to severe AE affecting >35% of body surface area	Serum cortisol levels	Baseline serum cortisol: pre- cosyntropin stimulation test 13.2 micrograms/dL (sd=6.1) post- cosyntropin stimulation test 35.3 micrograms/dL (sd=6.02) End of treatment serum cortisol: pre- cosyntropin stimulation test 12.4 micrograms/dL (sd=6.3) post- cosyntropin stimulation test 33.3 micrograms/dL (sd=8.1)	

Topical calcineurin inhibitors

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
Staab D;Kaufmann R;Brautigam M;Wahn U; 2005[110]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 195 Pimecrolimus cream 1% N = 129 Vehicle N = 66	Children included in a vehicle-controlled RCT of pimecrolimus (Breuer 2004,[300] Kaufmann 2004[301])	Pimecrolimus cream 1% applied twice daily vs vehicle applied twice daily	Outcomes at 4 Weeks: PQOL-AD psychosomatic wellbeing (mean score change) +0.3 (14.6%) vs +0.1 (6.2%), p<0.05 PQOL-AD effects on social life (mean score change)* +0.2 (6.5%) vs 0 (2%), p<0.05 PQOL-AD confidence in medical treatment (mean score change)* +0.3 (10%) vs +0.1 (3.5%), p<0.05 PQOL-AD emotional coping (mean score change) +0.4 (16.0%) vs +0.1 (6.5%), p<0.05 PQOL-AD acceptance of disease (mean score change) +0.3 (19.6%) vs +0.1 (6.9%), p<0.05	Source of Funding: Novartis *values estimated from graphs PQOL-AD: quality of life in parents and children with atopic dermatitis
McKenna SP;Whalley D;De PY;Staab D;Huels J;Paul CF;Assche D; 2006[109]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 384 Pimecrolimus cream 1% applied twice daily N = 283 Vehicle applied twice daily N = 101	Quality of life data for children included in two vehicle-controlled RCTs of pimecrolimus cream 1% (Wahn 2002[297] and Kapp 2002[302]). 154 infants included in the PIQOL-AD results 230 children in the PIQOL-AD results 144 children in the CDLQI results	Pimecrolimus cream 1% applied twice daily vs vehicle applied twice daily	Outcomes at 12 Months: PIQOL-AD (mean score change in infants) -4.9 (51%) vs -1.8 (21%) OR 1.8 (95% CI 1.12 to 2.92), p=0.016 PIQOL-AD (mean score change in children) -3.8 (41%) vs -2.3 (26%) OR 1.46 (95% CI 1.08 to 1.98), p=0.015 CDLQI (mean score change in children) 2.12 (95% CI 0.52 to 3.71), p=0.01	
Whalley D;Huels J;McKenna SP;van AD; 2002[296]	Study Type: Randomised Control Trial Evidence Level:	Total number of patients = 278 Pimecrolimus cream 1%	Children aged up to 8 years who were included in the Eichenfield 2002[295] study (n=278; 69% of	Pimecrolimus cream 1% applied twice daily vs vehicle applied twice daily	Outcomes at 6 Weeks: PIQoL-AD (mean change from baseline) -3.3 (35%) vs -1.3 (15%), p=0.023	Source of Funding: Novartis Pharmaceuticals Corporation Only results for 80% were available at 6 weeks.

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
	1+	N = 158 Vehicle N = 83	the total study population). Mean age about 4 years (range 1-7 years). Baseline mean PIQol-AD scores were 9.4 pimecrolimus vs 8.8 vehicle.		PIQoL-AD (least squares mean change) -3.20 vs -1.63 (difference 1.57, 95% CI 0.22 to 2.92)	Following the 6-week controlled phase, children from both groups were offered treatment with pimecrolimus for up to 6 months. QOL data at 6 months [EL=3] were also shown in the report, which indicated further reductions in scores (improvement).
Reitamo S;Harper J;Dbos J;Cambazard F;Bruijnzeel-Koomen C;Valk P;Smith C;Moss C;Dobozy A;Palatsi R; 2004[265]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 624 Tacrolimus ointment 0.03% once daily N = 207 Tacrolimus ointment 0.03% twice daily N = 210 Hydrocortisone acetate 1% N = 207	Children aged 2-15 years (mean about 7 years) with moderate-severe AE affecting 5% or more of BSA (mean 37-39%).	Tacrolimus ointment 0.03% applied once daily vs tacrolimus ointment 0.03% applied twice daily vs hydrocortisone acetate 1% applied twice daily	Outcomes at 3 Weeks: Modified EASI (median score change) 70% vs 78.7% vs 47.2%, p<0.001 both tacrolimus groups vs HC, p=0.007 between tacrolimus groups EASI (median score change) 66.7% vs 76.7% vs 47.6%, p<0.001 both tacrolimus groups vs HC, p=0.015 between tacrolimus groups Physician's global evaluation (at least 90% improvement) 27.8% vs 36.7% vs 13.6%, p value not reported Physician's global evaluation (at least 50% improvement) 74.1% vs 81% vs 52.9%, p value not stated Patient/parent's evaluation (% better or much better) 67% vs 82.9% vs 50.7%, p value no reported Itch (mean score change on 10cm VAS) -48% vs -57% vs -32%, p value not stated Sleep quality (mean change on 10cm VAS +27% vs +45% vs +25%, p value not reported Adverse effects* 23.2% skin burning 18.4% pruritus 3.9% folliculitis	Source of Funding: Fujisawa GmbH, Munich Treatment was given for 2 uninterrupted weeks, and for a further 7 days after clearance. Bath oil and nonmedicated emollients were permitted. Modified EASI includes an assessment of itch. *the most common adverse effects (occurring in 5% or more). Additionally skin infection occurred in 1.4% vs 2.9% vs 2.9%, p=NS

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
					2.9% flu syndrome vs 23.8% skin burning 21.4% pruritus 5.2% folliculitis 5.7% flu syndrome vs 14.5% skin burning, p=0.028 both tacrolimus groups vs HC 15.9% pruritus 3.9% folliculitis 5.3% flu syndrome	
Wahn U;Bos JD;Goodfield M;Caputo R;Papp K;Manjra A;Dobozy A;Paul C;Molloy S;Hultsch T;Graeber M;Cherill R;De PY;Flare Reduction in Eczema with Elidel (Children) Multicenter Investigator Study Group.; 2002[297]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 713 Pimecrolimus cream 1% N = 476 Vehicle N = 237	Children aged 1-17 years (mean 8 years) with atopic eczema affecting at least 5% of BSA (mean 24%), and IGA score of 2 or more on a 6-point scale; at baseline 26.2% pimecrolimus vs 27.8% vehicle had mild disease (score of 2), 55.3% vs 50.6% moderate, 15.6% vs 17.7% severe, 2.7% vs 3.8% very severe. Baseline EASI score 12.8 (mean). Exclusions: phototherapy or systemic therapy within 1 month	Pimecrolimus cream 1% applied twice daily (plus usual care)* vs vehicle applied twice daily (plus usual care)*	Outcomes at 12 Months: % with no flares of atopic eczema 50.8% vs 28.3%, p<0.001 Time to first flare 'significantly longer' in the pimecrolimus group; p<0.001. No numerical data EASI (median change from baseline, estimated from graph) -60% vs -40% % using TCS 42.6% vs 68.4% Duration of use: 57.4% vs 31.6% used 0 days 17.1% vs 27.5% used 1-14 days 25.5% vs 41% used for >14days Mean % time using TCS: 4.08% vs 9.10% Adverse effects 24.7% suspected drug-related adverse effect 28.9% nasopharyngitis 23% headache 13.2% bronchitis 14.6% influenza	Source of Funding: Novartis Pharma AG Double-blind. *treatment was applied to the affected areas at the first sign (erythema) or symptom (pruritus) of atopic eczema, to prevent progression to flare. Emollients were used in both groups to treat dry skin. Moderately potent TCS were mandated in both groups for flares not controlled by study medication (i.e. at least severe erythema and severe infiltration/papulation; IGA score of 4 or more). Treatment with TCS was followed by 1 week of treatment with study medication for 'residual disease'. 14.2% vs 7.0% used study mediation continuously. Antihistamines were permitted if the dosages used was stable; they were used by 57.2% of the pimecrolimus group vs 62.9% vehicle. Discontinuation rates at 12 months were 31.6% pimecrolimus vs 51.5% vehicle; p value was not reported, bu t the difference between groups was reported to be 'significant'. The main reason for discontinuation was unsatisfactory therapeutic effect (12.4% vs 30.4%).

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
					19.3% cough 15.4% pyrexia 10.5% application-site burning 14.2% bacterial skin infection 12.4% viral skin infection vs 18.7% suspected drug-related adverse effect 27.1% nasopharyngitis 21.5% headache 13.7% bronchitis 9.5% influenza 11.8% cough, p=0.04 11.8% pyrexia 9.3% application-site burning 30.9% bacterial skin infection 6.3% viral skin infection, p=0.038 RR of having a flare 0.69 (95% CI 0.61 to 0.77) Outcomes at 6 Months: % with no flares of atopic eczema 61% vs 34.2%, p<0.001	IGA was also measured as an outcome but no data were reported. Other than the adverse effects for which p values are given, no other statistically significant differences were reported between groups.
Kapp A;Papp K;Bingham A;Folster-Holst R;Ortonne JP;Potter PC;Gulliver W;Paul C;Molloy S;Barbier N;Thurston M;De PY;Flare Reduction in Eczema with Elidel (infants) multicenter investigator study group.;	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 250 Pimecrolimus cream 1% applied twice daily* N = 204 Vehicle* N = 46	Children aged 3-23 months (mean 12 months) with AE affecting at least 5% of BSA (mean 28%), and IGA score of 2 or more: 32.8% pimecrolimus vs 39.1% vehicle groups had mild disease, 57.4% vs 47.8% moderate, 8.3% vs 10.9% severe, 1.5% vs 2.2% very severe. Baseline EASI score was 12 (mean). Exclusions:	Pimecrolimus cream 1% applied twice daily* vs vehicle applied twice daily*	Outcomes at 12 Months: % with no flares of AE 56.9% vs 28.3% Time to first flare 'pimecrolimus was associated with a significantly longer flare-free period', p<0.001 Number of flares per person (mean) 1.0 vs 2.2, p<0.001 % using TCS 63.7% vs 34.8% used none. Duration of use 3.2% vs 6.2%	Source of Funding: Novartis Pharma AG Double-blind. *study medication was applied at the first sign (erythema) or symptom (pruritus) of AE, to prevent progression to flares. Emollients were used in both groups to treat dry skin. Moderately potent TCS were allowed in both groups for flares not controlled by study medication (IGA score of at least 4). Treatment with TCS was followed by a week of treatment with study medication for residual disease. 15.7% pimecrolimus vs 34.8% vehicle

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
2002[302]			immunocompromised, active skin infections, other skin infections or other infections that might interfere with the study.		IGA (score of 0 or 1) 53.9% vs 47.8%, p=NS EASI (mean score change) -7.3 (59%) vs -5.7 (45%) Pruritus (score of 0 or 1) 77% vs 63%, p=0.337 Adverse effects 6.5% application-site reactions 27% at least one skin infection vs 14.7% application-site reactions, p=0.104 27.6% at least one skin infection, p=0.728 Outcomes at 6 Months: IGA (score of 0 or 1) 52.9% vs 37.0%, p=0.03 % with no flares of AE 67.6% vs 30.4%	withdrew at 6 months, and 24.5% vs 39.1% at 12 months, p=0.016. IGA, pruritus and caregiver assessment all measured on a scale of 0-3.
Boguniewicz M;Fiedler VC;Raimer S;Lawrence ID;Leung DY;Hanifin JM; 1998[292]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 180 Tacrolimus ointment 0.03% N = 43 Tacrolimus ointment 0.1% N = 49 Tacrolimus ointment 0.3% N = 44 Vehicle N = 44	Children aged 7-16 years (mean about 10 years) with 5-30% BSA affected with AE (mean ranged from 15-19% across groups, p=0.049). Exclusions: in need of antimicrobial treatment	Tacrolimus ointment 0.03% applied twice daily vs tacrolimus ointment 0.1% applied twice daily vs tacrolimus ointment 0.3% applied twice daily vs vehicle applied twice daily	Outcomes at 22 Days: 75% improvement or more in physician's global assessment 69% vs 67% vs 70% vs 38%, p<0.004 for all tacrolimus groups vs vehicle EASI (% improvement in scores) 72% vs 77% vs 81% vs 26%, p<0.001 all tacrolimus group vs vehicle Head & neck total score (% improvement) 65% vs 83% vs 81% vs -2%, p<0.001 all tacrolimus groups vs vehicle Patients global assessment (% feeling better or much better)	

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
					76% vs 91% vs 91% vs 52%, p<=0.025 all tacrolimus groups vs vehicle Pruritus (% reduction in scores) no numerical data; 'significantly' greater for tacrolimus-treated patients vs the vehicle group, p=0.027 Adverse effects 20.9% burning 25.6% pruritus 0 erythema vs 10.2% burning 20.4% pruritus 2% erythema vs 6.8% burning 15.9% pruritus 4.5% erythema, p=NS for all between group differences Mean tacrolimus blood concentrations 0.07 ng/ml (SD 0.10) vs 0.09 ng/ml (SD 0.31) vs 0.18 ng/ml (SD 0.21) vs Outcomes at 4 Days: Mean tacrolimus blood concentrations 0.10 ng/ml (SD 0.17) vs 0.21 ng/ml (SD 0.32) vs 0.31 ng/ml (SD 0.41)	
Drake L;Prendergast M;Maher R;Breneman D;Korman N;Satoi Y;Beusterien KM;Lawrence I; 2001[294]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 323 Tacrolimus ointment 0.03% N = 1171 Tacrolimus ointment 0.1%	Children and toddlers included in the Paller 2001[293] study. 178 children mean age 9 years 145 toddlers (not defined), mean age 3 years.	Tacrolimus ointment 0.03% applied twice daily vs Tacrolimus ointment 0.1% applied twice daily vs Vehicle applied twice daily	Outcomes at 12 Weeks: CDLQI in children (mean score change)* -24.4 vs -24.1 vs -8.1, p=0.000 both tacrolimus groups vs vehicle, p=0.937 between tacrolimus groups CDLQI in toddlers (mean score change)* -30.8 vs -35.6 vs -7.9, p=0.000 both tacrolimus groups vs vehicle, p=0.224 between tacrolimus groups	Source of Funding: Fujisawa Healthcare *adjusted for baseline score. For the toddlers, relatives completed a version of the CDLQI (Toddler survey) modified based on recommendations from the developer.

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
		N = 118 Vehicle N = 116				
Eichenfield LF;Lucky AW;Boguniewicz M;Langley RG;Cherill R;Marshall K;Bush C;Graeber M; 2002[295]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 403 Pimecrolimus cream 1% N = 267 Vehicle N = 136	Children aged 1-17 years (mean 6.7 years) with atopic eczema affecting at least 5% of BSA (mean 26%), and IGA score of 2 or 3 (mild to moderate disease) on a 6-point scale. At baseline 30% pimecrolimus vs 31.6% vehicle had mild disease, 60.3% vs 57.4% moderate, 8.6% vs 8.1% severe, 1.1% vs 2.9% severe. Baseline EASI score 12.8 (mean).	Pimecrolimus cream 1% applied twice daily vs vehicle applied twice daily	Outcomes at 6 weeks: IGA (% with score of 0 or 1) 34.8% vs 18.4%, p <=0.05 Change in IGA score 59.9% vs 33.1% improved by 1 IGA score or more 36% vs 47.1% maintained baseline score 4.1% vs 19.9% worsened Change in EASI score -45% vs -1%, p<=0.001 Pruritus severity (% with score of 0 or 1; estimated from graph) 55% vs 33%, p<0.001 Patients assessment of disease control (% reporting complete or good control; estimated from graph) 61% vs 40%, p<0.05 Adverse effects 44% reported one or more 28% local adverse effects 14.2% URTI 13.9% headache 11.6% cough 10.1% nasopharyngitis 10.4% application-site burning 1.9% discontinuation due to adverse effects vs 42.6% reported one or more 35% local adverse effects 13.2% URTI 8.8% headache	Source of Funding: Novartis Pharmaceuticals Corp This report represents pooled analysis from 2 RCTs. Double-blind. IGA scored on a 6-point scale of 0-5, none to very severe. Pruritus was measured on a scale of 0-3, no itching/scratching to bothersome itching/scratching that disturbs sleep. Children also received stable doses of an additive-free basic, bland emollient for at least 7 days before baseline.

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
					8.1% cough 7.4% nasopharyngitis 12.5% application-site burning 2.9% discontinuation due to adverse effects	
Eichenfield LF;Lucky AW;Langley RG;Lynde C;Kaufmann R;Todd G;Lindsley L;Barbier N;Felser JM; 2005[306]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 589 Pimecrolimus cream 1% N = 390 Vehicle N = 199	Children included in vehicle-controlled RCTs of pimecrolimus cream 1% (Ho 2003[299] and Eichenfield 2002[295]). Results for children of Caucasian origin (54%) were compared with those for children of non-Caucasian origin (41.8% Black, 11.6% Asian, 46.6% 'other', mainly Hispanic)	Pimecrolimus cream 1% applied twice daily vs vehicle applied twice daily	Outcomes at 6 weeks: IGA score of 0 or 1 (Caucasian group) 45% vs 23.6%, p<0.02 (treatment effect 21.4, 95% CI 0.03 to 0.41) IGA score of 0 or 1 (non-Caucasian group) 36.3% vs 15.7%, p<0.001 (treatment effect 20.6, 95% CI 0.09 to 0.30) EASI (mean score change, Caucasian group) -6.56 (SD 8.24) vs -1.22 (SD 6.04), p<0.001 (treatment effect -4.35 95% CI -5.65 to -3.04) EASI mean score change (non-Caucasian group) -5.83 (SD 7.9) vs -0.49 (SD 9.34), p<0.001 (treatment effect -5.37, 95% CI -7.44 to -3.29) Adverse effects application-site burning: 9% (Caucasian) 5.6% (non-Caucasian) vs application-site burning: 9.1% (Caucasian) 10.1% (non-Caucasian)	Source of Funding: Novartis Pharmaceuticals Corp The proportions of children with an IGA score of 0 or 1 in the three non-Caucasian subgroups were also reported, as was the % change in EASI scores. IGA score of 0 or 1 (pimecrolimus vs vehicle): 34.2% vs 20.5% Black 42.9% vs 0% Asian 36.5% vs 15.0% other Mean EASI score change: -3.85 vs +0.28 Black -6.33 vs -0.32 Asian -7.41 vs +0.75 other
Ho VC;Gupta A;Kaufmann R;Todd G;Vanaclocha F;Takaoka R;Folster-Holst R;Potter P;Marshall K;Thurston M;Bush C;Cherill R;	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 186 Pimecrolimus cream 1% N = 123 Vehicle N = 63	Children aged 3-23 months (mean 12.6 months) with atopic eczema affecting 5% or more of BSA, and IGA score of 2 or 3 (mild or moderate) based on degree of erythema and infiltration/papulation; 32.5% pimecrolimus vs 33.3% vehicle groups	Pimecrolimus cream 1% applied twice daily vs vehicle applied twice daily	Outcomes at 6 weeks: IGA (score of 0 or 1) 54.5% vs 23.8%, p<0.001 EASI (mean score change) -6.81 vs -0.75, p<0.001 EASI (median % change) -81.6% vs -25%	Source of Funding: Novartis Pharmaceuticals Corp The 6-week randomised phase was double-blind. Following this, children were offered treatment with pimecrolimus cream 1% in an open, unblinded way. Emollients were permitted only on areas untreated with study medication. During weeks 7-26, emollients were permitted on all skin areas, but applied to treated areas

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
2003[299]			mild, 67.5% vs 66.7% moderate. Baseline EASI score 11.2 vs 10.2. Exclusions: phototherapy or systemic therapy for AE within 1 month, topical treatment or sedating antihistamine within 1 week, immunocompromised, concurrent or active skin disease or viral skin infections.		Pruritus severity (score of 0 or 1) 72.4% vs 33.3%, p<0.001 Carers assessment (complete or good control) 71.5% vs 27%, p<0.001 Adverse effects 31.7% pyrexia 23.6% URTI 14.6% nasopharyngitis 8.1% teething 8.1% diarrhoea 8.1% restlessness 7.3% gastroenteritis 5.7% bronchitis 5.7% influenza 4.9% rhinitis 5.7% asthma 0.8% bacterial skin infection vs 12.7% pyrexia, p<0.05 14.3% URTI 7.9% nasopharyngitis 4.8% teething 0% diarrhoea 4.8% restlessness 3.2% gastroenteritis 4.8% bronchitis 3.2% influenza 7.9% rhinitis 3.2% asthma 6.3% bacterial skin infection Outcomes at 26 Weeks: 54.7% had IGA score of 0 or 1 EASI score remained at about 80% below baseline	after study medication had been fully absorbed. 88.6% in the pimecrolimus group vs 52.4% in the vehicle group completed the 6-week DB phase. Pruritus score was measured on a scale of 0-3, no itching/scratching to bothersome itching/scratching that disturbs sleep.

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
					about 67% had absent/mild pruritus 27% pyrexia 21% URTI 16% nasopharyngitis 10% teething 9% bronchitis 9% otitis media	
Kempers S;Boguniewicz M;Carter E;Jarratt M;Pariser D;Stewart D;Stiller M;Tschen E;Chon K;Wisseh S;Abrams B; 2004[305]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 141 Tacrolimus ointment 0.03% applied twice daily N = 70 Pimecrolimus cream 1% applied twice daily N = 71	Children/ young people aged 2-17 years with moderate atopic eczema (Investigator's Global Assessment [IGA] score of 3 or more on a scale of 0-5). 83.6% were aged 2-12 years. Exclusions: treatment with phototherapy or systemic corticosteroids within 1 month, topical therapy (not specified) within 1 week, or systemic antibiotics within 2 weeks.	Tacrolimus ointment 0.03% applied twice daily vs pimecrolimus cream 1% applied twice daily	Outcomes at 4 Days: Application-site reactions 26% vs 24% Warmth/burning/stinging 17% vs 2-%, p=0.931 (% with duration >30 mins: 67%) vs 0, p<0.001) Erythema or irritation 19% vs 8%, p=0.039 (% with duration >30 mins: 85%) vs 0, p<0.001) Increased itching 20% vs 8%, p=0.073 (% with duration >30 mins: 60%) vs 17%, p=0.559) Outcomes at 6 weeks: IGA score of clear or almost clear 42% vs 30%, p=0.119 Pruritus score of absent or mild 70% vs 64%, p=0.493 % body surface area affected % change from baseline: -45% whole body -35% head/neck -42% lower limbs -38% upper limbs -36% trunk	Source of Funding: Novartis Pharmaceuticals Corporation The primary outcome in the study was local tolerability. Data for day 4 were presented in detail in the report because these reactions 'are most common during the first few days of therapy'. Incidence appeared to fall with time in both groups over the 6-week study period (data shown in graphs only). Ease of application also reported. Data not reproduced here. Discontinuation rates 4% tacrolimus vs 18% pimecrolimus.

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
					vs % change from baseline: -43% whole body -54% head/neck -29% lower limbs -35% upper limbs -40% trunk	
Paller A;Eichenfield LF;Leung DY;Stewart D;Appell M; 2001[293]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 351 Tacrolimus ointment 0.03% N = 117 Tacrolimus ointment 0.1% N = 118 Vehicle N = 116	Children aged 2-15 years (61% aged 2-6 years, 39% 7-15 years), with moderate (38%) or severe (62%) AE involving 10-100% BSA (mean 45-49%). 83% had AE on head or neck. Exclusions: other skin conditions, pigmentation, or scarring, infected AE	Tacrolimus ointment 0.03% applied twice daily vs Tacrolimus ointment 0.1% applied twice daily vs Vehicle applied twice daily	Outcomes at 12 weeks: Success (improvement of 90% or more on physician's global assessment) 35.9% vs 40.7% vs 6.9%, p<0.001 both tacrolimus groups vs vehicle EASI (mean score change) -14 vs -15 vs -2, p<0.001 both tacrolimus groups vs vehicle (values estimated from graph) Pruritus (mean score change) -4 vs -4 vs -0.8, p<0.001 tacrolimus groups vs vehicle (values estimated from graphs) Patient's global assessment No numerical data. Statistical significance reported for both tacrolimus groups vs vehicle, p<0.001 % BSA affected (mean change) -26% vs -27% vs -6%, p<0.001 both tacrolimus groups vs vehicle (values estimated from graph) Adverse effects 43% skin burning 41% pruritus 5% varicella 4% vesiculobullous rash 3% sinusitis vs 34% skin burning 32% pruritus 1% varicella	Source of Funding: Fujisawa Healthcare Emollients permitted on unaffected areas. Discontinuation rates due to adverse effects: 5% tacrolimus 0.03%, 2.5% tacrolimus 0.1%, 8% vehicle. Incidence of herpes simplex reported for tacrolimus groups combined and vehicle (2.6% vs 0.9% respectively). Incidence of molluscum contagiosum also 2.6% vs 0.9%. Median duration of treatment (days): 85 tacrolimus 0.03%, 85 tacrolimus 0.1%, 46 vehicle. Mean quantities used per day: 4.6g, 4.1g, 7.4g.

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
					1% vesiculobullous rash 1% sinusitis 29% skin burning, p=0.04 vs tacrolimus 0.03% 27% pruritus, p=0.03 vs tacrolimus 0.03% 0% varicella, p=0.042 vs tacrolimus 0.03% 0% vesiculobullous rash, p=0.042 vs tacrolimus 0.03% 8% sinusitis, p=0.046 vs tacrolimus 0.1% Tacrolimus blood concentrations No measurable concentration in 90% of 148 samples. Mean and median levels below limit of quantification (2ng/ml) at all time points. Range of values 0-2.28ng/ml.	
Reitamo S;Van Leent EJ;Ho V;Harper J;Ruzicka T;Kalimo K;Cambazard F;Rustin M;Taieb A;Gratton D;Sauder D;Sharpe G;Smith C;Junger M;De PY; 2002[266]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 560 Tacrolimus ointment 0.03% N = 189 Tacrolimus ointment 0.1% N = 186	Children aged 2-15 years (mean about 7 years) with moderate to severe AE affecting 5-60% BSA (mean 23-26%). Exclusions: skin disorders other than AE, history of eczema herpeticum	Tacrolimus ointment 0.03% applied twice daily vs Tacrolimus ointment 0.1% applied twice daily vs Hydrocortisone acetate 1% applied twice daily	Outcomes at 3 Weeks: Modified EASI (median score change) -55.2% vs -60.2% vs -36.0%, p=0.006 both tacrolimus groups vs HC, p=0.006 between tacrolimus groups Physician's global evaluation (at least 90% improvement) 38.5% vs 48.4% vs 15.7%, p=0.001 both tacrolimus groups vs HC, p=0.055 between tacrolimus groups Tacrolimus blood concentrations 23.4% levels below limit of quantification 75% <=1ng/ml 1.6% 1to <5ng/ml vs 12.4% levels below limit of quantification 76.3% <=1ng/ml 11.3% 1to <5ng/ml Adverse effects 18.5% skin burning 13.2% pruritus 5.8% folliculitis 3.2% skin infection 2.1% skin erythema vs	Source of Funding: Fujisawa GmbH, Munich Double-blind. Bath oils and non-medicated emollients were allowed. Modified EASI includes assessment of itch. Of the tacrolimus blood concentrations, levels of 1ng/ml or more were seen in 1.6% of the tacrolimus 0.03% group, and 11.3% of the tacrolimus 0.1% group at some time point. No values exceeded 5ng/ml. Lower limit of quantification was not reported.

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
					20.4% 11.3% 4.3% 2.2% 0.5% vs 7.0%, p<0.05 both tacrolimus groups vs HC 7.6% 2.7% 2.2% 1.6%	
Siegfried E;Korman N;Molina C;Kianifard F;Abrams K; 2006[304]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 275 Pimecrolimus cream 1% N = 183 Vehicle N = 92	Children aged 3 months to 11 years (mean 39 months) with mild to severe AE (IGA score 2-4) involving 5% or more BSA (mean 29%). Mean IGA score 2.9 (scale 0-5 none-severe), mean pruritus severity score 1.9 (scale 0-3, none-severe). Exclusions: immunocompromised children, concurrent skin disease, AE triggered by a known unavoidable allergen or irritant, active viral or bacterial infection.	Pimecrolimus cream 1% applied twice daily* vs vehicle applied twice daily*	Outcomes at 6 Months: % with no major flares 51.9% vs 34.1%, p=0.007 Mean duration of TCS use (days) 10.9 vs 17.3, p=0.002 Adverse effects 9.8% rhinorrhoea vs 2.2%, p=0.025	Source of Funding: Novartis Pharmaceuticals Corp Double-blind study. Emollients were applied to all areas of dry skin. *used at the first sign or symptom of AE, plus a 'major flare regimen' was introduced if after 7 days pimecrolimus or vehicle plus emollient the condition had not improved, or worsened to a point where IGA 4 or more. A TCS (fluticasone propionate cream 0.05% or mometasone furoate 0.1% cream [the latter in children aged over 2 years]) was used at night during a flare, while pimecrolimus or vehicle continued to be used in the morning. The major flare regimen was used until all signs or symptoms of AE resolved or for a maximum of 3 weeks, after which twice daily use of pimecrolimus or vehicle resumed. 7% pimecrolimus vs 23% vehicle experienced more than 2 major flares. Withdrawal rates 18% pimecrolimus vs 28% vehicle, due to unsatisfactory therapeutic effect in 3.8% vs 14.3%, p=0.003.

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
						Rhinorrohoea was the only adverse effect occurring in significantly different proportions of children. Others were predominantly respiratory and gastrointestinal effects. Application-site reactions were the most common suspected drug-related adverse effects (2.2% in both groups). Score change for EASI and pruritus were only reported for day 8; data not reproduced here.
Sikder M;Al MS;Khan RM;Chowdhury AH;Khan HM;Hoque MM; 2005[267]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 45 Clobetasone butyrate cream 0.05% N = 15	Children aged 7-15 years with moderate-severe AE affecting 5-50% BSA (mean 25%). Exclusions: other skin conditions, history of eczema herpeticum	Tacrolimus ointment 0.03% applied twice daily vs Clobetasone butyrate 0.05% applied twice daily vs Tacrolimus ointment 0.03% (evening) + clobetasone butyrate 0.05% (morning)	Outcomes at 4 Weeks: Modified EASI (median score change) -81.9% vs -95.1% vs -98.7%, p=0.00 vs tacrolimus, p=0.018 clobetasone vs tacrolimus, p=NS clobetasone vs combination % BSA affected (mean change) -40% vs -66.7% vs -83.3%, p=0.00 vs tacrolimus, p=0.007 clobetasone vs tacrolimus, p=NS clobetasone vs combination Investigator's global evaluation (at least 90% improvement) 13.3% vs 66.7% vs 93.3%, p value not reported Adverse effects 46% skin burning 20% itching vs 7% 13.3% vs 46%, p=0.010 tacrolimus vs clobetasone, p=0.042 clobetasone vs combination 6.7%, p=0.562	
Breuer K;Braeutigam M;Kapp A;Werfel T;	Study Type: Randomised Control Trial	Total number of patients = 196	Children aged 3-23 months (mean 12 months) with AE affecting at least 5% of	Pimecrolimus cream 1% applied twice daily vs vehicle applied twice daily	Outcomes at 16 Weeks*: No numerical data for efficacy outcomes; but reported to be sustained. Adverse effects believed to be related to treatment:	Source of Funding: Novartis Pharma AG Double-blind.

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
2004 [300]	Evidence Level: 1+	Pimecrolimus cream 1% N = 130 Vehicle N = 66	BSA, and IGA score of 2 or more; 9.3% pimecrolimus vs 12.1% vehicle had mild AE, 58.1% vs 59.1% moderate, 26.4% vs 25.8% severe, 6.2% vs 3% very severe. Baseline EASI score 17 (mean). Exclusions: 'insufficient washout' from other treatments for AE, concomitant disease that might interfere with the study, severe concurrent skin disease, active viral or bacterial infections		6 children (2 cases of impetigo, 1 herpes simplex dermatitis, 1 varicella, 1 asthma, 1 aggravated atopic eczema, 1 exacerbated eczema). Outcomes at 4 Weeks: EASI (mean score change) -71.5% vs +19.4%, p<0.001 EASI (mean score change in components) -61.5% infiltration -60.3% excoriation -54% erythema -37.1% lichenification vs -4.3% infiltration +24.1% excoriation +7.4% erythema +10.5% lichenification (all p<0.001 vs pimecrolimus) IGA (mean score change) -50.7% vs -5.5%, p<0.001 IGA (score of 0 or 1) 53.5% vs 10.6%, p<0.001 SCORAD (mean score change) -55.2% vs +1.1%, p=0.002 Pruritus severity (mean score change) -59% vs +16%, p<0.001 Sleep loss (mean score change) -57% vs +5%, p<0.001 Dry skin (mean change in % with) -27.1% vs -5.3%, p<0.1 Adverse effects	Emollients were only permitted on areas not treated with study medication. Correlations between changes in EASI, IGA and SCORAD scores were also reported - data not reproduced here. Adverse effects were reported in a related publication (Kaufmann 2004[301]). Drop-out rates: 10% pimecrolimus, 38% vehicle. *after 12 weeks open-label, uncontrolled use.

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Population characteristics	Comparison	Results and comments	Reviewer comment
					63.8% reported at least one 2.3% treatment-related (1 application-site burning, 1 impaired healing, 1 burning sensation) vs 60.6% reported at least one 3.0% treatment-related (1 application-site burning, 1 erythema)	
Schachner LA;Lamerson C;Sheehan MP;Boguniewicz M;Mosser J;Raimer S;Shull T;Jaracz E;US Tacrolimus Ointment Study Group.; 2005[307]	Study Type: Randomised Control Trial Evidence Level: 1+	Total number of patients = 317 Tacrolimus ointment 0.03% N = 158 Vehicle N = 159	Children aged 2-15 years (mean about 7 years) with mild to moderate AE affecting 2-30% of BSA (mean 12%). Baseline EASI score 6, itch score 5 (on scale 0-10). Exclusions: other skin conditions, previous use of tacrolimus ointment	Tacrolimus ointment 0.03% applied twice daily vs vehicle applied twice daily	Outcomes at 6 Weeks: IGA (% with score of 0 or 1) 50.6% vs 25.8%, p<0.0001 EASI (mean score change) -54.8% vs -20.8%, p=0.0004 % BSA affected (change) -50.5% vs -16.4%, p<0.0001 Itch (mean score change) -2.8 (57%) vs -1.2 (24%), p<0.0001 Adverse effects 19% burning/stinging 23.4% itching 7.6% erythema 2.5% withdrew due to application-site reactions 1.3% folliculitis 2.5% skin infections 1.3% acne 0 eczema herpeticum vs 17% 33.3%, p=0.05 18.9%, p=0.003 7.5%, p=0.04 3.8% 3.1% 0% 0.6% eczema herpeticum	Source of Funding: Astellas Pharma US Double-blind study. Nonmedicated emollients were allowed on non-affected areas. Tacrolimus was used on the head and neck (areas affected in 54% and 59% of children respectively). Withdrawal rates were 18.4% tacrolimus vs 38.4% vehicle, p<0.0001; 2.5% vs 12.6% due to lack of efficacy, p=0.0007.

Bibliographic information	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes	Comments
Hanifin JM;Paller AS;Eichenfield L;Clark RA;Korman N;Weinstein G;Caro I;Jaracz E;Rico MJ; 2005[312]	Study Type: Case series Evidence Level: 3	To evaluate the long-term safety and efficacy of tacrolimus ointment.	Total No. of Patients = 799 Tacrolimus ointment 0.1% (185 aged 2-6 years, 206 aged 7-15 years)	Children 2-15 years and adults who participated in a previous clinical trial of tacrolimus ointment 0.1% for mild to severe AE. Tacrolimus was applied twice daily to affected areas, continuing for a week after clearance of these areas. 30-35% of children's BSA was affected. Exclusions: other skin conditions.	Outcomes at 49 Months: Adverse effects in children 2-15 years 20% pruritus 13% pustular rash 19% skin burning 8% skin erythema 23% skin infection: 5.3% herpes simplex 7% warts 5.4% varicella zoster 8% molluscum contagiosum 0.3% eczema herpeticum	
Koo JYM;Fleischer Jr AB;Abramovits W;Pariser DM;McCall CO;Horn TD;Gottlieb AB;Jaracz E;Rico MJ; 2005[310]	Study Type: Case series Evidence Level: 3	To evaluate the safety and efficacy of tacrolimus ointment in children and adults.	Total No. of Patients = 7923 Children (2-15 years) N = 3959 Adults N = 3964	Children aged 2-15 years and adults with mild to severe AE treated with tacrolimus ointment 0.03% or 0.1% twice daily to affected areas, and continued for one week after clearance of affected area. BSA affected 36%. Exclusions: other skin conditions	Outcomes at 6 Months: Adverse effects 17% pruritus 19% skin burning 15% skin infection 6.5% skin erythema	Source of Funding: Astellas Comments: Emollients permitted on non-treatment areas. Median study duration 210 days (1-687), mean 239 days (135 for tacrolimus 0.03% and 247 for tacrolimus 0.1%). 26% discontinued treatment. Efficacy data (% BSA affected) not reproduced here. <4% were prescribed TCS for AE at some time point, and 7% for any reason. Adverse effects occurring in more than 5% were allergic reaction (e.g. conjunctivitis, seasonal allergy, food allergy), asthma, cough, fever, flu-like symptoms, headache, infection, otitis media, pharyngitis, sinusitis. Data on infections reported for overall group (children and adults): 1.3% varicella zoster, 2.3% herpes simplex, 1.3% warts, 0.9% molluscum contagiosum, 0.3% eczema herpeticum

Bibliographic information	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes	Comments
Kaufmann R;Folster-Holst R;Hoger P;Thaci D;Loffler H;Staab D;Brautigam M;-Study Group.; 2004[301]	Study Type: Case series Evidence Level: 3	To assess the efficacy and safety of longer-term use of pimecrolimus.	Total No. of Patients = 188 Pimecrolimus cream 1% N = 188	Children included in Breuer 2004,[300] who were offered 12 weeks' open-label use of pimecrolimus cream 1% after the 4-week DB randomised phase	Outcomes at 12 Weeks: EASI (mean score change) no numerical data; 'significant improvements sustained' Adverse effects 73% reported one, 4% of these treatment-related: 4 infections 1 asthma 1 aggravated AE* 1 exacerbated eczema*	Source of Funding: Novartis Pharma AG Comments: This extension study provides little data on safety or efficacy of 12-weeks' pimecrolimus use. *terms not defined
Lakhanpaul M;Davies T;Allen BR;Schneider D; 2006[318]	Study Type: Case series Evidence Level: 3	To measure the systemic absorption of pimecrolimus after 1 years' use.	Total No. of Patients = 5 Pimecrolimus cream 1% N = 5	Children aged 6-12 months, included in the Allen 2003[317] study who were followed up for 1 year in total.	Outcomes at 12 Months: Mean blood pimecrolimus concentration 0.68 (SD 0.76) ng/ml Outcomes at 6 Months: Mean blood pimecrolimus concentration 0.32 (SD 0.35) ng/ml	Source of Funding: None declared Comments: pimecrolimus was used as required: mean duration of use (days) was 332 (range 168-365). Two children were also treated with TCS during the study. Lower limit of quantification of blood pimecrolimus concentrations was 0.1ng/ml.
Lubbe J;Friedlander SF;Cribier B;Morren M;Garcia-Diez A;Gelmetti C;Hofmann H;Houwing RH;Kownacki S;Langley RGB;Virtanen M;Wolff K;Wisseh S;McGeown C;Abrams B;Schneider D; 2006[315]	Study Type: Case series Evidence Level: 3	To assess safety and efficacy of pimecrolimus used in everyday practice.	Total No. of Patients = 947 Pimecrolimus cream 1% N = 947	Children and adults aged 3 months to 81 years with AE of any severity. Median age 8 years; 62% were aged up to 12 years. Exclusions: active viral infections at treatment site, other skin conditions, treatment with immunosuppressive therapy or phototherapy.	Outcomes at 6 Months: IGA (% with reduction in whole-body score) 66% aged <2 years 71% aged 2-12 years IGA (% with reduction in facial score) 78% aged <2 years 79% aged 2-12 years IGA (% with whole-body score of 0 or 1) 54% aged <2 years 48% aged 2-12 years 76% aged <2 years 80% aged 2-12 years Duration and quantity of pimecrolimus use	Source of Funding: Novartis Comments: Pimecrolimus was used in addition to standard care (emollients, treatment for infections as per physician's usual practice, TCS used to treat flares at the physician's discretion). 85% received concomitant treatment for AE (no details other than for TCS, which were used at least once by 53%). 88% were using emollients at baseline, 80% after bathing/showering, which fell to 53% at 6 months. Pimecrolimus was applied twice daily to affected areas at the first signs or symptoms of AE and continued as long as signs or symptoms of the disease

Bibliographic information	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes	Comments
					135.6 mean days use (75%) mean quantity used 4.2g per day daily use in 55% Adverse effects* 15.7% nasopharyngitis 14.6% URTI 10.5% cough 10.2% pyrexia 5.2% application site burning 3.7% pruritus 3.0% impetigo 2.0% worsening AE 1.7% molluscum contagiosum 0.8% herpes simplex infections 0.3% skin papilloma	persisted; the aim of treatment was to prevent progression to flare). Data for children aged up to and including 12 years extracted here. 16% discontinued early, 10% due to loss of follow-up or unsatisfactory therapeutic effect, and 2.3% due to adverse effects. *Those occurring in more than 10%, and those related to skin or skin infections listed here
Papp KA;Werfel T;Folster-Holst R;Ortonne JP;Potter PC;De PY;Davidson MJ;Barbier N;Goertz HP;Paul C; 2005[303]	Study Type: Case series Evidence Level: 3	Assess long-term efficacy and safety of pimecrolimus (up to 2 years).	Total No. of Patients = 91 Pimecrolimus cream 1% N = 91	Children from the study Kapp 2002[303] who were offered continued treatment with pimecrolimus cream 1% for a further year. Mean age 28 months (range 18-41 months). IGA scores: 14.3% =0, 22% =1, 24.2%=2, 36.2%=3, 3.3%=severe, 0 = very severe. Of the 91 enrolled, 76 had been treated with pimecrolimus in the RCT, and 15 with vehicle.	Outcomes at 2 Years: % with no flares 76.9% % using TCS 27.5% (mean duration of use 7.5 days) IGA score of 0 or 1 71.4% EASI (mean score change from year 1 to 2) -50% Total BSA affected (mean change year 1 to 2) -42%	Source of Funding: Novartis Pharma AG Comments: Pimecrolimus was applied to affected areas at the first sign or symptoms of disease flare. The use of moderately potent TCS was also permitted for flares uncontrolled by pimecrolimus. 2 years' use refers to the 1-year DB RCT and this 1 year follow-up phase. 16% had previously been treated with vehicle rather than pimecrolimus. Over the 2 years, 57.9% of those treated with pimecrolimus had not used TCS. Median duration of pimecrolimus use = 99 days (range not quoted).
Staab D;Pariser D;Gottlieb AB;Kaufmann R;Eichenfield LF;Langley RG;Scott	Study Type: Case series Evidence Level:	To evaluate systemic exposure to pimecrolimus.	Total No. of Patients = 21 Pimecrolimus cream 1%	Children 3-23 months (mean 12 months) with AE affecting 50% BSA (range 10-92%).	Outcomes at 3 Weeks: % blood samples within given concentration 31% <0.1ng/ml 40% 0.1 to <0.5ng/ml	Source of Funding: none declared Comments: Pimecrolimus was applied to all skin

Bibliographic information	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes	Comments
G;Ebelin ME;Barilla D;Schmidli H;Burtin P; 2005[316]	3		N = 21		15% 0.5-1.0ng/ml 10% >1.0-2.0ng/ml 2% >2.0-2.26ng/ml 96% of the 100 blood samples were below 2ng/ml.	areas, including face and neck. Emollients were used to treat dry skin areas and affected areas after pimecrolimus had been 'visibly absorbed'. Mean quantity of pimecrolimus used per application ranged from 1g to 8.5g. Blood samples taken on days 1 and 10, collected 1 and 2 hours, or 2 and 3 hours after application of study medication. Limit of quantification = 0.1ng/ml. The relationship between BSA and pimecrolimus blood concentrations were also considered (data shown graphically) - the difference in mean concentrations of pimecrolimus between children with 10% and 90% BSA affected was 0.4ng/ml.
Allen BR;Lakhanpaul M;Morris A;Lateo S;Davies T;Scott G;Cardno M;Ebelin ME;Burtin P;Stephenson TJ; 2003[317]	Study Type: Case series Evidence Level: 3	To measure pimecrolimus blood concentrations and report efficacy and tolerability of pimecrolimus.	Total No. of Patients = 26 Pimecrolimus cream 1% N = 26	Children aged 4 months to 14 years with 21-80% BSA affected by atopic eczema.	Outcomes at 3 Weeks: % blood samples within given concentration 44% 0-0.5ng/ml 33% 0.5-1.0ng/ml 21% 1.0 to <2.0ng/ml 2% 2.0-2.6ng/ml Blood pimecrolimus concentrations in relation to BSA Mean difference between concentrations for where 10% or 90% BSA affected: 0.7ng/ml On linear regression analysis, blood concentration increased with increased BSA affected, p=0.028	Source of Funding: none declared Comments: Use of bland emollients was encouraged (applied 1 hour after pimecrolimus). Blood concentrations measured on days 4 and 22. The lower limit of quantification was 0.5ng/ml. It was reported that there was 'no evidence of accumulation' between days 4 and 22 (results were in a similar range on graph).
Tan J;Langley R; 2004[311]	Study Type: Case series Evidence Level: 3	To evaluate the safety and efficacy of tacrolimus used for 6 months	Total No. of Patients = 236 Tacrolimus ointment 0.1% in children N = 83	Children or adults aged 2 years or older who had used tacrolimus ointment 0.1% twice daily for mild to severe AE. Exclusions: other skin	Outcomes at 6 Months: Adverse effects in children 2-15 years 32% skin infections: 6.1% folliculitis 13.4% impetigo	Source of Funding: Fujisawa Canada Comments: Itch and BSA affected were also reported - data not reproduced here.

Bibliographic information	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes	Comments
				conditions.	6.1% 'other' application site 2.4% herpes simplex 2.4% molluscum contagiosum 1.2% fungal infection 1.2% nail infection Application-site effects: 38.1% burning 33.9% pruritus 19.9% infection 9.3% paraesthesia 5.1% warmth	

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Study summary	Reviewer comment
Bieber T; Vick K; Folster-Holst R; Belloni-Fortina A; Stadler G; Worm M; Arcangeli F; 2007 308	Study Type: Randomised comparative trial Evidence Level: 1-	Intervention: Patients applied 0.03% tacrolimus ointment twice daily or 0.1% methylprednisolone aceponate (MPA) ointment in the evening over all affected areas for a minimum of 2 weeks and maximum of 3 weeks and cleared areas were treated for an additional 7 days post clearance. Comparison: comparison between 0.03% tacrolimus and 1% MPA	n=265 children and adolescents of which n=129 were randomised to MPA or n=136 to tacrolimus MPA group n=96 (74%) were age 11 years or less Tacrolimus n=102 were age 11 years or less n=257 of children and adolescents completed the study	Children and adolescents with severe and very severe atopic eczema three age groups:2-6, 7-1 and 12-15 years mean ages MPA = 7.8 ±4.2 years tacrolimus = 7.5 ±4.2 years	IGA score EASI Modified EASI (mEASI) for patients BSA Patients' assessment of itch (VAS), quality of sleep (VAS), cost effectiveness of treatment and assessment of change of disease from baseline. CDLQI Safety assessment by physical examination, record of other medications, pregnancy tests, medical history and monitoring of AEs throughout study.	Results were reported as a whole for all age groups. IGA: IGA score was 'clear' or ' almost clear' by the end of treatment in 86/129 (67%) in the MPA group and 91/136 (67%) in the tacrolimus group p=0.9314 EASI: By end of treatment the mean % change was 90% in the MPA group compared with 85% in the tacrolimus group p=0.0667 mEASI: Data were reported to reflect the EASI score but was not given. BSA : %BSA was ~29% at baseline and dropped to 6.8% in the MPA group and 7.7% in the tacrolimus group. Patients' assessment of itch was 68.0mm to 6.3 mm in the MPA group and 63.6mm to 13.8mm with tacrolimus at the end of the study p=0.0004 Patients' assessment of sleep was 54.6mm to 5.3mm in the MPA group and 51.5mm to 11.0mm in the tacrolimus group from baseline to end of treatment. P=0.0094. Medication costs: Mean cost for MPA treatment was 14.59 Euros and 100.99 Euros for	The authors concluded that both treatments had a similar efficacy in the treatment of severe atopic eczema but suggested that the severity index (EASI), sleep and itch data shown increased benefit of MPA over tacrolimus which made it a more favorable treatment as it is also significantly cheaper.	Comparative study which showed both treatments were of benefit to children with severe atopic eczema [EL=1-] Presentation of data was selective. The comparative cost of the two treatments was significant. This study was sponsored by Intendis GmbH Berlin.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Study summary	Reviewer comment
						tacrolimus treatment during the study. P=0.0001 CDLQI data was reported in favour of MPA over tacrolimus in terms of 'symptoms and feelings 'and 'sleep' but no data was shown. n=0 of the MPA and n=2 in the tacrolimus group reported a worsening of their atopic eczema during the study.		
Arkwright PD; Gillespie MC; Ewing CI; David TJ; 2006 309	Study Type: Cohort within patient left-right side (arms and legs) comparison Evidence Level: 2-	Intervention: One set of arms and legs were treated with their usual topical corticosteroid (hydrocortisone 1%, flucinolone acetonide 0.00625%, clobetasone butyrate 0.05%, betamethasone valerate 0.025% or 0.1%, hydrocortisone butyrate 0.1% or mometasone furoate 0.1% for 7 days. The opposite side of the body was treated with 0.03% tacrolimus ointment twice a day for 7 days. If the 0.03% tacrolimus ointment had no effect after 7 days, it was stepped up to 0.1% tacrolimus for a further week Comparison: Side to side body comparison	n=96 children	Children aged 6 months to 18 years were recruited (no mean available but data suggests all children participating were 12 years or below) with moderately severe atopic eczema. This was defined as incomplete control of atopic eczema from emollients and topical corticosteroids.	Severity of atopic eczema as determined by clinical examination regarding erythema and lichenification (visual and by touch) Classifications: less severe, no difference and more severe between sides.	After 7 days 48/93 children had a greater improvement with 0.03% tacrolimus compared with their usual topical corticosteroid. The remaining 45 children for whom 0.03% tacrolimus was no more effective than their usual treatment were given a further weeks treatment of 0.1% tacrolimus. After the second week with 0.1% tacrolimus 24/45 (53%) showed a more marked improvement compared with their usual treatment. Overall tacrolimus ointment (0.03% and 0.1%) was more effective than usual topical corticosteroid treatment in 72/93 children (77%).	Topical tacrolimus (0.03% or 0.1%) was found to be more effective than topical corticosteroid treatment in 77% of children who completed a side to side body comparison study.	This study lacked detail on demographic data, diagnosis and outcome measures. [EL=2-] There were also no safety data. The funding of this study was undeclared.
Remitz A; Harper J; Rustin M; Goldschmidt WFM; Palatsi R;	Study Type: Longitudinal case series	Intervention: 0.03% topical tacrolimus ointment twice daily to affected areas of	n=466 of which n=328 completed the study.	Children aged 2-15 years (no details but split into two age groups 2-6 and 7-15	Safety assessments of adverse events and laboratory tests (haematology, renal	Mean study duration was 16.3 SD 6.4months On average children used tacrolimus	There was a significant improvement in the children's atopic	This is a large and longer term uncontrolled case series and shows

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Study summary	Reviewer comment
van der Valk PGM; Sharpe G; Smith CH; Dobozy A; Turjanmaa K. 2007 313	Evidence Level: 3	body. If improvement did not occur within 2 weeks, children in the verum group were provided with 0.1% tacrolimus. If this failed to work at 2 weeks, children were excluded at investigator's discretion. Comparison: None		years) with moderate and severe atopic eczema (50/50) as defined by Hanifin and Rajka.	and hepatic function) at day 1, 6 and 12 months and at the end of study. Children's weight and height. EASI IDQOL CDLQI	on 64% of the study days. Safety Most common AE was pruritus and skin burning. Other AEs assessed as causally related were skin infection, lack of drug effect, skin erythema, folliculitis, herpes simplex, application site reaction, rash, skin neoplasm benign, flu syndrome and pustular rash. 33 children (7.1%) experienced a serious AE, this lead to discontinuation of treatment in 15 patients (3.2%). One 6 year old boy had leukopaenia with no accompanying symptoms and was withdrawn from study. Eosinophil levels were greater in 40% of the study population No other abnormalities were seen in the biochemical tests. No growth retardation was seen during the study. Efficacy: Both age groups improved (EASI), with notable effect by 2 weeks and was maintained throughout study (data in graph form only) Physician's assessment of therapeutic response was 73-77% of patients experiencing at least a satisfactory response to treatment by the end of the study. This was reflected in the QoL scores (IDQOL,CDLQI) (also presented in graph form only)	eczema within 2 weeks of use of the tacrolimus ointment and this was maintained throughout the study. Adverse events do occur with tacrolimus treatment with local irritation being the most prevalent however all adverse events were transient.	that the efficacy is maintained over time and the safety profile is similar to that of shorter studies. [EL=3] This study was funded by a grant from Fujisawa GmbH
Singalavanija S; Noppakin N; Limpongsanuru	Study Type: Case series	Intervention: 0.03% tacrolimus (Protopic®) twice daily for 4 weeks	n=61 of which n=58 completed the study	Children (mean age 6.98 ±2.81 years) with moderate (n=29) or	Physician's Global Evaluation of Clinical Response	PhGECR significantly increased from week 1 to week 4 (2.28,3.07	Topical 0.03% tacrolimus is effective in treating	Uncontrolled case series of short duration.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results and comments	Study summary	Reviewer comment
k W; Wisuthsarewong W;Aunhachoke K; Chunharas A; Wananukul S; Akaraphanth R. 2006 314	Evidence Level: 3	on affected areas or until one week after the affected areas had cleared. Minimum length of treatment 2 weeks. Comparison: None		severe (32) atopic eczema as defined by Hanifin and Rajka criteria.	(PhGECR) EASI Patient's Global Evaluation of Clinical Response (PaGECR) CDLQI (Thai version) Safety assessment of adverse events	respectively, p<0.001) PhGECR at week 4 rated 7% clear, 26% excellent, 40% marked, 21% moderate and 4% slightly improved. EASI significantly decreased 6.09 at baseline, 2.09 at week 4 (p<0.001). PaGECR significantly increased between week 1 and week 4 (1.91, 2.31 respectively, p=0.018). PaGECR at week 4 rated 57% much better, 26% better, and 12% slightly better, 3% the same, 2% worse. Mean CDQoL scores significantly decreased from 1.19 to 0.68 at end of study (p<0.01). Adverse events reported application site burning (n=14), erythema (n=2), itching (n=10), folliculitis (n=1) and infection (n=2).	moderate to severe eczema over a 4 week period. Most adverse events (burning sensation, erythema, and pruritus and itching) were resolved after 1 week.	Safety issues of longer or repeated application of treatments not addressed.[EL=3] The funding of the study was undeclared

Dry bandages and medicated dressings (including wet wrap therapy)

See above (emollients and bandages)

Antihistamines and other antipruritics

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
La Rosa M;Ranno C;Musarra I;Guglielmo F;Corrias A;Bellanti JA; 1994[338]	Study Type: RCT Evidence level: 1+	22 children Cetirizine, n=11* Placebo, n=11 Exclusions: chronic disease of kidney, liver or cardiovascular system; using other oral antihistamine treatment; cutaneous or other infections	Children with atopic eczema with mild to moderate itching Aged 6-12 years, mean 7 years (SD 2) Diagnosis by Hanifin and Rajka	Intervention: Cetirizine 5mg per day for 8 weeks in children weighing 30kg or less, and 10mg per day for 8 weeks in children over 30kg. Plus concomitant treatment including disodium cromoglycate and procaterol Comparison: Placebo for 8 weeks Plus concomitant treatment including topical corticosteroid and disodium cromoglicate	Follow-up period: Duration of treatment, 8 weeks Outcome Measures: 1) Clearance of all signs and symptoms 2) Concomitant treatment (% children using) 3) Adverse effects	1) 73% vs 18%, p<0.02 2) 18% cetirizine vs 82% placebo, p<0.01 Children in cetirizine group used disodium cromoglycate and procaterol, and those in the placebo group 'consisted mainly' of disodium cromoglicate aerosol and nasal and cutaneous administration of topical corticosteroids. 3) 'no adverse effects of cetrizine were noted'	This study reported significant differences between groups, with fewer children treated with cetirizine using concomitant treatment, and more cetirizine-treated children experiencing clearance of all signs and symptoms of eczema.	Funding: UCB Pianezza (Turin) Italy supplied the medicine Method of randomisation and degree of blinding unclear. *originally 12 children were randomised to cetirizine, 1 withdrew 'voluntarily' therefore analysis was undertaken on 11 from each group Severity of pruritus (cetirizine vs placebo, total scores) also measured by dividing the body into 20 areas and each area into 7 manifestations: pruritus, erythema, vesiculation, palpus, excoriation, scaly crusts and lichenification; an arbitrary score for manifestation in each body area is recorded, ranging from 1=none, 2 = mild, 3=moderate, and 4=severe. However, data were only presented in a graph in the trial report, with no statistical analysis of between group differences, although confidence intervals on the graph showed overlap between cetrizine and placebo groups at all time points measured, indicating no statistically significant difference between groups. Erythema also measured using the same scale as for severity; again no numerical data reported.
Munday J;Bloomfield R;Goldman M;Robey H;Kitowska GJ;Gwiezdziski Z;Wankiewicz A;Marks	Study Type: RCT Evidence level: 1+	151 children Chlorphenamine, n=75 Placebo, n=76	Children with atopic eczema including nocturnal itching and scratching. Severity of itching at baseline: chlorphenamine 1.3% none, 20% minimal, 56% mild, 22.7%	Intervention: Chlorphenamine 1mg/2.5 ml for children aged 1-5 once daily, and 2mg/5ml for those aged 6-12 once daily in the	Follow-up period: Duration of the treatment, 4 weeks Outcome Measures: 1. Severity of nocturnal itching rated at day 29 (modal response; % chlorphenamine vs	1. 56% vs 56.6% none 33% vs 29% minimal 8% vs 10.5% mild 1.3% vs 2.6% moderate 1.3% vs 1.3% no data, p=0.745 overall	No significant differences were seen between chlorphenamine and placebo in any outcomes (severity of nocturnal itching, investigator's	Funding: none declared. Multi-centre DB RCT (UK and Poland) Itching severity recorded by investigator using a 5-point rating scale (none to severe)

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
R;Protas-Drozd F;Mikaszewska M; 2002[339]		Exclusions: systemic antihistamine treatment in last 2 weeks; history of epilepsy, glaucoma, or hepatic disease; any other clinical abnormalities the investigator believed would affect the trial	moderate, 0 severe; placebo 0 none, 19.7% minimal, 59.2% mild, 15.8% moderate, 5.2% severe. Aged 1-12 years, median 7 years	evening, before bedtime. 3 hours after first administration, additional second dosage permitted if necessary After 2 weeks of trial children allowed to take double previous dosage if itching had not improved (2mg/5ml for children aged 1-5 years and 4mg/10 ml for those aged 6-12 years) Plus concomitant treatment including the use of emollient (Unguentum Merck) and mild topical corticosteroids (hydrocortisone cream 1%) as required Comparison: Placebo matching test medicine in appearance and smell Plus concomitant treatment including the use of emollient and mild topical corticosteroids	placebo) 2. Investigator assessment of atopic eczema signs and symptoms (median VAS scores) 1) Baseline Total score A. Erythema B. Excoriation C. Dryness D. Lichenification E. Exudation and crusting 2) End of treatment Total A. Erythema B. Excoriation C. Dryness D. Lichenification E. Exudation and crusting 3. Concomitant treatment 1) Quantity of emollient used (g), from 100g container 2) Quantity of hydrocortisone 1% used (g), from 30g container 4. Safety	2. Severity of atopic eczema (chlorphenamine vs placebo, 95% CI for median difference) 1) Baseline (median VAS scores) Total: 28 vs 26, 95% CI -5.0 to 2.0, p=0.479 A. 30 vs 24, 95% CI -10 to 1.0, p=0.192 B. 20 vs 20, 95% CI -3.0 to 4.0, p=0.6 C. 50 vs 48, 95% CI -6.0 to 6.0, p=0.91 D. 30 vs 28, 95% CI -7.0 to 2.0, p=0.283 E. 0 vs 0, 95% CI 0 to 0, p=0.634 2) End of treatment Total: 14 vs 14, 95% CI -3.6 to 1.6, p=0.532 A. 10 vs 7, 95% CI -8.0 to 0, p=0.05 B. 6 vs 0, 95% CI -3.0 to 0, p=0.066 C. 30 vs 30, 95% CI -6.0 to 7.0, p=0.798 D.14 vs 20, 95% CI -1.0	assessment of eczema, quantity of emollient or hydrocortisone 1% used).	Investigators recorded severity of atopic eczema by assessing five symptoms on a digital VAS; erythema, excoriation, dryness, lichenification, exudation and crusting. Last observation carried forward used for children who withdrew from the study early.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				(hydrocortisone cream 1%) as required		to 8.0, p=0.296 E. 0 vs 0, 95% CI 0 to 0, p=0.096 3. Concomitant treatment (quantity used; chlorphenamine vs placebo) 1) 64.5g vs 68g, median difference 2, 98% CI -5.0 to 12.0, p=0.517 2) 15.0g vs 13.0g, median difference 0, 98% CI -3.0 to 2.0, p=0.968 4. 13% (20/151) of children reported a total of 29 separate adverse events in both treatment arms, of which none were serious. Events were not described.		
Klein GL;Galant SP; 1980[340]	Study Type: RCT Evidence level: 1+	20 Hydroxyzine n=10 Cyproheptadine n=10 Exclusions: children who had previously shown adverse reactions to either drug.	Children with acute exacerbation of atopic eczema (present for at least 24 hours but no longer than 7 days). Any antipruritics stopped for 4 days before trial started. Aged 2-16 years, mean 8.95 years hydroxyzine vs 8.35 years cyproheptadine. Baseline day pruritus score (mean, SEM): 2 (0.3) hydroxyzine vs	Intervention: Hydroxyzine 1.25mg/kg/day three times per day with maximum of 30mg/day three times per day for 7 days Plus use of lubricating cream three times daily (Lubriderm) Comparison: Cyproheptadine 0.25mg/kg/day	Follow-up period: Duration of treatment, 7 days Outcome Measures: 1. Severity of pruritus 1) nocturnal pruritus 2) day pruritus 2. Physician's evaluation of dermatitis 3. Adverse effects	1. Severity of pruritus (hydroxyzine vs cyproheptadine, mean % improvement in scores) 1) 48.8% (SEM 3.39) vs 30.1% (4.9), p<0.005 2) 32.1% (4.98) vs 6.2% (4.9), p<0.001 2. Scores at endpoint (hydroxyzine vs cyproheptadine)	This study found that hydroxyzine was more effective than cyproheptadine in reducing day and night pruritus over a period of 1 week in children with atopic eczema who were also using an emollient	Funding: Roerig Pfizer Pharmaceuticals. Double-blind study. No details of methods of randomisation and concealment. SEM=standard error of the mean. Severity of pruritus graded using: mild (1 point), itching occasionally bothersome; moderate (2 points), itching occurs often but not enough to alter daily activity or sleep; severe (3 points), itching frequent enough to disturb daily activity or sleep.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
			1.6 (0.2) cyproheptadine; night pruritus score 2.7 (0.16) vs 2.4 (0.22)	three times per day with maximum of 6mg/day three times per day for 7 days Plus use of lubricating cream three times daily (Lubriderm)		1.7 (0.48) vs 0.5 (0.49), p<0.05 3. Sedation in n=2 vs n=3 (hydroxyzine vs cyproheptadine)		Physician's evaluation of atopic eczema used the following scoring system: -1= worse (increase of erythema, excoriation), 0= no change (in lesion), 1= slight improvement (decrease of erythema), 2=moderate improvement (decrease in erythema and excoriation), 3=marked improvement (decrease of erythema, excoriation, and size of lesion). No other antihistamines, antipruritics or anxiolytics were permitted during the study period, nor topical corticosteroids.
Yoshida H, Niimura M, Ueda H et al 1989[341]	Study Type: RCT Evidence level: 1-	284 randomised (255 analysed for efficacy) Ketotifen n=145 (131 analysed) Clemastine n=139 (124 analysed)	Individuals, mean age 9 years (SD 0.7) with atopic eczema; 24% mild, 65% moderate, 11% severe. Exclusions: received treatment with systemic corticosteroids during the 2 weeks prior to the study; dermatologic symptoms disappeared or changed quickly.	Intervention: Ketotifen 0.2mg/ml Dosage according to body weight; for those <14kg, dose 2ml twice daily; for those 14kg or more and <23kg, 3ml twice daily; for those 23kg or more, 5ml twice daily. Comparison: Clemastine 0.1mg/ml Dosage according to body weight; for those <14kg, dose 2ml twice daily; for those 14kg or more and <23kg, 3ml twice daily; for those 23kg or more, 5ml twice daily.	Follow-up period: Duration of treatment (4 weeks) Outcome Measures: 1) Investigator's global improvement rating* 2) Investigator's rating of improvement in five symptoms A. itching B. erythema/papule C. weeping eczema/erosion D. excoriation/scratch E. lichenification 3) Adverse effects	1) markedly improved 13.1 ketotifen vs 8.1% clemastine moderately improved 43.8 vs 22.8%, p<0.001 slightly improved 16.2% vs 32.5% unchanged 16.2% vs 13.8% slightly aggravated 6.2% vs 11.4% moderately aggravated 3.1% vs 8.1% markedly aggravated 1.5% vs 3.3% 2) % having improvement in symptoms (ketotifen vs clemastine) A. 79.2% vs 57.3%, p<0.01 B. 73% vs 57.8%, p<0.05 C. 70.7% vs 53.6%, p<0.10 D. 70.4% vs 54.3%, p<0.05	This poor quality study with loosely defined endpoints does not provide useful data regarding the comparative effectiveness of ketotifen and clemastine	Funding: none declared Multicentre DB study [EL=1-] because fewer analysed than randomised, and poor consideration of whether groups balanced at baseline White vaseline (white soft paraffin) was permitted, and hydrocortisone 0.25% ointment if needed for 'serious symptoms' *Seven grades: markedly improved, moderately improved, slightly improved, unchanged, slightly aggravated, moderately aggravated, markedly aggravated

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						E. 54.5% vs 48% no p value given 3) % reporting: 9.8% vs 13.2%. Drowsiness 'most frequent' event; no numerical data reported		
Diepgen TL;Early Treatment of the Atopic Child Study Group; 2002 Aug[343]	Study Type: RCT Evidence level: 1++	795 Cetirizine n=398 Placebo n=397 Exclusions: young children with asthma; weight below the third percentile; chronic pulmonary disease; severe neurologic or psychological disorder; cardiac disease; prior desensitisation or immunotherapy; taken part in a clinical trial within 3 months	Children aged 12-24 months with active symptoms of atopic eczema at least 1 month before the trial started and at least one parent or sibling with a history of atopic eczema, allergic rhinitis or asthma. Mean age 16.8 months in the cetirizine arm and 17.2 months in the placebo arm. Mean SCORAD scores 24.9 cetirizine, 25.1 placebo	Intervention: Cetirizine 0.25mg/kg twice daily for 18 months Plus concomitant medication: topical or systemic therapy including emollients, topical corticosteroids and other oral antihistamine agents if necessary Comparison: Placebo (matching cetirizine in appearance and taste) twice daily for 18 months Plus concomitant medication: topical or systemic therapy including emollients, topical corticosteroids and other oral antihistamine agents if necessary	Follow-up period: duration of treatment, 18 months Outcome Measures: 1. Severity of atopic eczema (SCORAD) 1) Cetirizine 2) Placebo 3) Cetirizine vs placebo 2. Use of topical and systemic medications during the trial (% patients taking other medications) 1) Emollient 2) NSAI cream 3) Tar (not specified whether coal tar) 4) Mild topical corticosteroid 5) Moderate to potent topical corticosteroids	1. Severity of atopic eczema (mean baseline vs end of the treatment SCORAD scores [% change]) 1) 24.9 vs 15.2, p<0.001 (39%) 2) 25.1 vs 15.7, p<0.001 (37%) 3) 'no statistically significant difference between groups' (no details reported) 2. Use of topical and systemic medications during the trial (cetirizine vs placebo) 1) 76.9% vs 76.1%, p=0.79 2) 14.1% vs 13.9%, p=0.93 3) 14.3% vs 14.4%, p=0.99 4) 41.7% vs 41.6%,	This study found that incidence of urticaria was significantly lower in the cetirizine group. Other outcomes did not differ significantly between groups (disease severity, usage of other treatments for eczema). However, usage of other oral antihistamines was significantly lower with cetirizine than with placebo. In the subgroup of children with more severe atopic eczema, the mean percentage days' use of moderate to potent topical corticosteroids was significantly lower in the cetirizine group.	Funding: UBB, S.A. Kits for determination of immunochemistry parameters were supplied by Pharmacia & Upjohn. This RCT was a multi-centre study involving 12 European countries and Canada (the Early Treatment of the Atopic Child [ETAC]). Its aim was to establish whether cetirizine could delay the onset of asthma in young children with eczema. Double-blind. Drop-out rates: 12% cetirizine, 12.8% placebo. There were no recommendations or restrictions for the treatment of eczema during the trial period. A symptom or event was counted as urticaria when typical hives or areas of skin swelling, redness and itching, distinctly different from the child's usual inflammatory skin lesions to atopic eczema, were reported.[346] Quantities of other medications taken were not reported.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
					6) Other oral antihistamine	p=0.17		
					7) Antibiotics/antiseptics	5) 53.5% vs 56.4%, p=0.41		
					3. Duration of use of topical and systemic medications during the trial (mean % days of use during 18 month trial period)	6) 18.6% vs 24.9%, p=0.03		
						7) 21.1% vs 25.2%, p=0.17		
					1) Emollient	3. Duration of use of topical and systemic medications during the trial [(mean %), cetirizine vs placebo]		
					2) NSAI creams			
					3) Tar			
					4) Mild topical corticosteroid	1) 59.5% vs 58.6%, p=0.894		
					5) Moderate to potent topical corticosteroids	2) 7.3% vs 5.9%, p=0.828		
					6) Other oral antihistamine	3) 7.4% vs 7.7%, p=0.971		
					7) Antibiotics/antiseptics	4) 22.2% vs 20.5%, p=0.801		
					4. Subgroup data on children with SCORAD > 25 (n=347)	5) 18.8% vs 25.2%, p=0.067		
					1) Duration of use of topical corticosteroids (mean % days of use of other medication)	6) 3.4% vs 4.4%, p=0.035		
						7) 4.5% vs 6.2%, p=0.146		
					Mild topical corticosteroid			
					Moderate to potent topical corticosteroids	4. Subgroup data on children with SCORAD > 25 (n=347)		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
					2) Local antibiotics/antiseptics 5. % having one or more episodes of urticaria	1) Duration of use of topical corticosteroids [(mean %), cetirizine vs placebo) 28.1% vs 23.1%, p=0.366 (mild) 25.8% vs 35.1%, p=0.014 (moderate to potent) 2) 45% vs 64%, p=0.037 5. 5.8% cetirizine vs 16.2% placebo, p<0.001		
Wahn U 1998 544	Study Type: RCT Evidence level: 1++	795 Cetirizine n=398 Placebo n=397	As for Diepgen 2002[343]	Intervention: As for Diepgen 2002[343] Comparison: As for Diepgen 2002[343]	Follow-up period: 18 months treatment and follow-up Outcome Measures: 1) Asthma incidence 2) Urticaria incidence	1) 37.7% cetirizine vs 38% placebo RR 1.0 (95% CI 0.8 to 1.2), p=0.973 In subgroups, significant differences identified for those with raised IgE levels due to grass pollen and/or house dust mite: grass pollen (n=70), 27.8% vs 58.8%, RR 0.5 (95% CI 0.3 to 0.90), p=0.002 house dust mite (n=124), 28.6% vs 51.5%, RR 0.6 (95% CI 0.3 to 0.9), p=0.005 grass pollen and house dust mite (n=158), 34.2% vs 53.7%, RR 0.6 (95% CI 0.4 to 0.9),	Overall risk of asthma was not significantly different in cetirizine and placebo groups, but differences were apparent in the subgroups with raised IgE levels to grass pollen and/or house dust mite.	Funding: as for Diepgen 2002[343]

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						p=0.006 2) 5.8% vs 16.1%, p<0.001		
Simons FE; 1999 Aug 344	Study Type: RCT Evidence level: 1++	As for Diepgen 2002[343]	As for Diepgen 2002[343]	Intervention: Cetirizine 0.25mg/kg twice daily for 18 months Plus concomitant medication: topical or systemic therapy including emollients, topical corticosteroids and other oral antihistamines if necessary Comparison: Placebo (matching cetirizine in appearance and taste) twice daily for 18 months Plus concomitant medication: topical or systemic therapy including emollients, topical corticosteroids and other oral antihistamine agents if necessary	Follow-up period: Duration of treatment, 18 months Outcome Measures: Safety 1. Young children with serious symptoms/events (%) 2. Hospitalisations (%) 3. Neurological symptom or event 1) Insomnia 2) Fatigue 3) Somnolence 4) Hyperkinesia 5) Nervousness 6) Emotional lability 7) Febrile convulsions 8) Ataxia (loss of balance) 9) Others 10) Total 4. Behavioural and developmental assessments 1) Behavioural screening questionnaire assessment (semi-structured interview to answer 12 different behaviour characteristics of early childhood; in	Safety (cetirizine vs placebo) 1. 9.3% vs 13.6% p=0.053 2. 9% vs 11.8% p=0.189 3 Neurological symptom or event 1) 9% vs 5.3%, p=0.071 2) 3.3% vs 1.3%, p=0.093 3) 2.3% vs 2.0%, p=1.0 4) 1.3% vs 2.3%, p=0.296 5) 1.3% vs 1.8%, p=0.577 6) 1.3% vs 1.5%, p=0.772 7) 0.5% vs 1%, p=0.45 8) 0.5% vs 0.5%, p=1.0 9) 1.3% vs 1.5%, p=0.772 10) Total 16.3% vs 13.8%, p=0.373 4. Behavioural and developmental assessments (total mean scores) 1) 6.32 vs 6.51 p=0.604 (cetirizine arm, n=168,	The incidence of serious adverse events and neurological adverse effects was not significantly different between cetirizine and placebo groups. There did not appear to be any effect on behaviour or development in the subgroup of patients evaluated for these outcomes.	Funding: See Diepgen 2002[343] Double-blind RCT Drop-out rates: 12% cetirizine, 12.8% placebo Compliance 'greater than 90%' in both groups 'Serious' adverse events - as defined by the World Health Organisation

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
					n=322 [41%]) 2) The McCarthy Test (scale of children's abilities for the assessment of psychomotor development in young children aged 2.5 years and older; in n=161 [20%]) 5. Electrocardiogram results 6. Laboratory tests	placebo arm, n=154) 2) 103 vs 103.6 (cetirizine arm, n=83, placebo arm, n=78) 5. All within normal limits 6. No clinical relevant difference found between two arms		
Stainer et al. 2005 [336]	Study Type: RCT Evidence level: 1+	114 Aqueous lotion containing sodium cromoglicate 4%, n=58 Placebo (lotion base only), n=56	114 children aged 2-12 years with moderate to severe atopic eczema (SCORAD >= 25 and <= 60) Usual treatment with emollients and topical corticosteroids continued during the study	Intervention: sodium cromoglicate 4% Comparison: placebo	Follow-up period: 12 weeks Outcome Measures: 1. Severity of atopic eczema (SCORAD) 2. Use of topical corticosteroids 3. Patient opinion 4. Adverse events	1. Baseline SCORAD (mean +- SD) sodium cromoglicate 4%, 41.0 +- 9.0 placebo, 40.4 +- 8.73 Reduction in SCORAD after 12 weeks: sodium cromoglicate 4%, 13.2 (36%) placebo, 7.6 (20%) (mean difference 5.6, 95% CI 1.0 to 10.3) Clinically relevant treatment success*: sodium cromoglicate 4%, 50% placebo, 30% (OR 2.29, 95% CI 1.06 to 4.94) Treatment-related adverse events: sodium cromoglicate 4%, 7/58 placebo, 4/56		*Clinically relevant treatment success defined as reduction in severity (SCORAD) of at least 25% with no accompanying increase in topical corticosteroid use

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						(irritation, redness or burning at site of application).		
Chunharas A;Wisuthsarewong W;Wananukul S;Viravan S; 2002 Apr 342	Study Type: Cohort Evidence level: 2+	50 (48 analysed) Mometasone furoate 0.1% cream plus loratadine syrup, n=24 Mometasone furoate 0.1% cream plus placebo syrup, n=24	Children with atopic eczema who an affected are at least 4cm2, and severity scores (SCORAD) of at least 10 out of 18 (mean was 12); pruritus of the target area present, with a minimum score of 2.5 (scale 0-3), mean was ~2.7 Age 2-11.2 years, mean 6.2 years Exclusions: history of hypersensitivity to either drug, or nonresponsive to mometasone before the study. If antibiotics or antihistamine were used or severe illness and side effects were noted, the patient was withdrawn from the study.	Intervention: Loratadine syrup once daily (5ml if weight up to 30kg, 10mls if over 30kg) in addition to mometasone furoate 0.1% cream, applied once daily after a bath in the evening Comparison: Placebo syrup once daily (5ml if weight up to 30kg, 10mls if over 30kg) in addition to mometasone furoate 0.1% cream, applied once daily after a bath in the evening	Follow-up period: Duration of treatment, 15 days Outcome Measures: 1. Severity of the disease (% change in SCORAD score from baseline) 2. Physician global assessment Cleared=100% improvement Marked=75-100% improvement Moderate=50-75% improvement Slight=<50% improvement No change Exacerbation 3. Pruritus score (0= none to 3=severe; % change from baseline) 4. Adverse effects	1. -84% loratadine vs -85% placebo, p=0.883 (actual score change 12.4 to 1.94 vs 12.21 to 1.83) 2. 75% vs 91.6% had 75-100% improvement, p=0.245 8.3% vs 8.3% had 50-75% improvement, p=1.0 17% vs 0% had <50% improvement, p=0.109 3. -90% vs -97% (from 2.77 to 0.29 vs 2.63 to 0.09), p=0.097 4. No reports of drowsiness or difficulty awakening 1 child from each group reported dizziness 1 vs 0 nausea 0 vs 1 anorexia	It appears that addition of loratadine to mometasone furoate has no added benefit.	Funding: none declared. The study is described as a double-blinding, multicentre trial, however, the methods of blinding are unclear. Two children from the loratadine group withdrew (1 due to impetigo, 1 because rash 'very much improved') Although the volume (and not strength) was reported in the paper, it is assumed that the only available proprietary preparation of loratadine was used (5mg/5ml).

Bibliographic information	Study type and evidence level	Aim of study	Number of patients	Population characteristics	Outcome measures	Results and comments	Study summary	Reviewer comment
Bettzuege-Pfaff BI, Melzer A 2005[242]	Case series EL=3	Intervention: Bath oil containing soya oil and lauromacrogols (Balneum Plus bath oil). No specific instructions were given regarding quantity or frequency of use. 13% used the bath oil daily, 38% three times a week, 42% twice a week, and 7% once a week. 78% received additional treatment ('mostly other basic preparations' in 50.1%, topical preparations containing urea in 41.9%, and topical steroids in 27.9%). Comparison: No comparison group	3566	Paediatric patients with dry, itchy dermatoses. 94% were aged under 15 years, 83% under 9 years, and 61% aged 4 years or under. Atopic eczema was the most common skin condition being treated (86%). Level of skin dryness was moderate or severe in 89%, and the level of pruritus moderate or severe in 75%.	1) Physician rated severity 2) Global assessment of success of treatment regimen 3) Physician assessment of compliance 4) Physician assessment of tolerability 5) Adverse effects	1) Change in score (% mean reduction) -62% (-69% in those [21%] who only used bath oil 2) 14.3% symptoms cleared (score 0) 82.6% improvement (drop in total score) 2.0% no change 1.1% deterioration 3) 'good/very good' in 90% 4) 'good/very good' in 96.8% 5) 0.28% skin reactions ('mostly mild skin reactions such as burning, itching, reddening of the skin')	This case series reports improvement in the skin condition of mainly paediatric patients with dry, itchy dermatoses treated with a bath oil containing soya oil and lauromacrogols. Skin reactions occurred in 0.28% over the mean duration of treatment of 6 weeks.	Funding: Hermal Kurt Herrmann GmbH, Reinbek, Germany. This was a post-marketing surveillance study. Physician-rated severity (assessing skin dryness, itching, flaking, excoriation); 0=none, 1=slight, 2=moderate, 3=severe. Global assessment of tolerability: very good, good, moderate or poor. Compliance also rated globally using same criteria.

Treatment for infections associated with atopic eczema

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Kubeyinje EP; 1995 [397]	Study Type: Case-control Evidence level: 2-	n=32 children with atopic eczema and with a varicella infection n= 34 children unaffected by atopic eczema and with a varicella infection	Children with atopic eczema (no details of severity)consisted of 20 males and 12 females mean age = 3.2, age range 1-12 years Children unaffected by atopic eczema consisted of 23 males and 11 females mean age 3 years, age range 1-11 years	Intervention: none Comparison: Clinical data concerning the varicella infection between the children with atopic eczema and those children unaffected by atopic eczema	Follow-up period: Duration of disease Mean 16 days +/- 3.6SD Outcome Measures: Prodromal features (fever and general malaise) Persistent fever Profuse eruption Severe pruritus Secondary bacterial infection Pneumonia Bronchiolitis Duration of illness	unaffected group vs. atopic eczema group Prodromal features: 14.7%, 12.5% Persistent fever 5.9%, 37.5%* Profuse eruption 5.9%, 31%* Severe pruritus 17.6%, 87.5%* Secondary bacterial infection 5.9%, 31%* Pneumonia 0,1 Bronchiolitis 0,2 Duration of illness 11 days +/- 3.4,16 days +/- 3.6** *p<0.01, ** p<0.01 statistically significant difference between groups	This study suggests that varicella infection is more aggressive in children with atopic eczema compared with children unaffected by eczema. Symptoms were more severe, secondary complications were more likely and the duration of disease was longer.	This is an isolated study on a small population of children with atopic eczema (severity unknown). It high-lights potential problems with atopic eczema and varicella infection. [EL=2-] The funding of this study was undeclared.
Williams H; 1993 [368]	Study Type: Case-control Evidence level: 2+	n=9263 children	Children involved in the National Child Development Survey for whom the presence or absence of visible eczema (no details of severity) and warts were recorded at the ages of 11 and 16 years	Intervention: none Comparison: Comparison between children with atopic eczema and children unaffected by atopic eczema and the prevalence of viral warts.	Follow-up period: Data was collected at 11 and 16 years for each child. Outcome Measures: The prevalence of visible warts	The prevalence of visible warts at age 11 and or 16 years was less in children with atopic eczema compared with unaffected children: 5.4% 95% CI 3.0 to 7.7 8.7% 95% CI 8.1 to 9.3 respectively. Relative risk for development of warts in children with atopic eczema 0.60; 95% CI 0.37 to 0.95; p=0.03 This effect persisted even	This study does not support the hypothesis that there is an increased risk of viral warts in children with atopic eczema.	This is a large study but was not designed to investigate the prevalence of viral warts and atopic eczema in children. These data were extracted retrospectively. Although viral warts were slightly more prevalent in the non-atopic eczema population this is probably not of clinical significance. [EL=2+] This study was part of the National Child Development Survey.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						when confounding factors such as region of residence, ethnic group, social class, and family size were considered. This effect was not influenced by whether eczema was 'active' (visable) or 'inactive' at the time of examination		
Weinberg E;Fourie; 1992 416	Study Type: RCT Evidence level: 1-	n=33 of which n=16 received active treatment n=17 received placebo n=3 in the active group were withdrawn due to side effects, non-compliance and the presence of a resistant organism	Children aged 6 months to 12 years suffering with *S.aureus* superinfected AE	Intervention: Oral cefadroxil in suspension 50mg/kg/day in two equal doses Comparison: Oral placebo in suspension	Follow-up period: 2 weeks Outcome Measures: Skin swab sensitivity cultures from 3 sites Hanafin/Rajka activity scores Pictorial documentation RAST for egg albumin , cow's milk and *S.aureus* Total serum IgE, IgA, Ig G IgM 0-3 grading of eczema activity Patient and physician global evaluation	28/30 patients had superinfections of *S.aureus* or *S.aureus* and mixed group b haemolytic streptococcus as diagnosed by swabs at start of study Only one case was resistant to cefadroxil. At 2 weeks: 0/30 in the active group and 9/17 in the placebo group had clinically apparent superinfections. 4/30 in the active group and 14/17 in the placebo had positive cultures 45.5% of the active group were classified as severe compared to 84.6% at baseline. 37.5% of the placebo group were classified as severe compared to 82.4% at baseline.	This study suggests that cefadroxil is a useful antibacterial agent for superinfected atopic eczema when *S.aureus* is involved.	This is small, probably unblinded RCT [EL=-1] particularly of note is the difference between physician and patient global assessment at 2 weeks. The funding of this study was undeclared.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						There were no intergroup difference in symptoms of atopic eczema Immunoglobulin serum levels were unchanged during the study. One AE: emesis with active treatment patient withdrew Physician rated global assessment was significantly in favour of the active treatment (p=0.009) Patient rated global assessment was similar in both groups.		
Kimata H; 1999 Nov 417	Study Type: Cohort Evidence level: 2-	n=35 children of which n=17 were controls (2-11 months old) and n=18 active treatment (2-11 months)	Children (< 1 year old) with atopic eczema (no details of severity) and a MRSA infection.	Intervention: Nadifloxacin (15-30g) and bufexamac ointment (20-40g) Comparison: Bufexamac ointment (30-60g)	Follow-up period: 4 weeks of study plus 3 months for active group Outcome Measures: IgE serum levels measured using anti SEA and anti-SEB antibodies Skin scores for inflammation 0 (none) 1(erythema only) 2 (erythema with swelling) on 15 areas of the body. Skin culture identification of MRSA Blood samples for haematological, hepato-renal function	Active group: Serum levels of anti SEA IgE (before 0.6 SD 0.4 after 0.3 SD 0.1, p<0.001) and anti SEB IgE (before 0.8 SD 0.3after 0.3 SD 0.1, p<0.0001) were significantly improved MRSA was absent from all cultures and for 3 months after Atopic eczema significantly improved (before 20.0 SD 4.0, after 9.0 SD 3.0, p<0.0001) Control group: No changes in anti SEA (before 0.5 SD 0.3 after 0.6 SD 0.4) and anti SEB (before 0.7 SD 0.4 after 0.8	This study suggests that nadifloxacin is effective for the treatment of MRSA with atopic eczema in children. There were no adverse events in the short duration of this study.	Small studies with no inter group comparisons. No long term data on the potential safety issues of using nadifloxacin although assumably treatment would always be short term. The funding of this study was undeclared.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
					and urine taken before and after treatment	SD 0.4) IgE levels MRSA still present in all cases Atopic eczema did not improve (before 19.0 SD 5.0, after 18 SD 4.0) No nephropathy or hepatoxity was noted from blood and urine samples		
Hjorth N; Schmidt H; Thomsen K; 1985 419	Study Type: Controlled double-blind Left-right body comparison Evidence level: 2-	n=81 patients of whom n=26 were children	60/81 patients had a diagnosis of atopic eczema (no details, or individual number for children). The mean age of the children was 9 years (range 1-15 years). Children under 2 years of age were excluded. ' The majority of the patients enrolled were clinically judged to be have a certain degree of impetiginised dermatosis.'	Intervention: On a randomised basis the patients received the combination of 0.1% betamethasone 17-valerate and 2% microcrystalline fusidic acid ('Fusicort') on the right hand side of the body and 0.1% betamethasone 17-valerate on the left side of the body or vice versa twice daily for 7 days. The cream vehicle was the one used in the commercial preparation of 'Betnovate' Comparison: Left-right comparison on the individuals body.	Follow-up period: One week Outcome Measures: At visit 1(time 0) and visit 2 (1 week later): A bacterial swab was taken from a lesion on either side of the body. Clinical symptoms were rated on a scale of 0-3 severity scale taking into account: vesicles, oedema, erythema, excoriation, crusting, lichenification and itching. In additional at visit 2 the overall effect of the treatment was assessed as 'cleared', 'improved', 'unchanged' or 'worse' and treatment preference if any was recorded.	No individual data for children There was no difference in overall clinical evaluation of the two treatments made by the investigator at the end of one week. 'Success' was recorded in 53 cases with the combination treatment and 45 cases after betamethasone alone. 'Failure' was recorded in 3 and 5 cases respectively. Mean symptom score was reduced from 12.4 to 3.1 with the combination nad from 12.5 to 3.6 by steroid alone (no SD or significance level available). 46/81 preferred the combination and 34 of the 46 considered the combination to be more effective. ($p<0.05$). Positive isolates of Gram-	This study showed no clinically superiority of the combined treatment of fusidic acid and betamethasone on the clinical improvement of impetiginised atopic eczema in children and adults. Both groups improved with little evidence to suggest differing reduction in Gram - positive bacteria and patient preference for either treatment	This small study was short in duration did not present separate children and adult data. No details were given as to the degree of severity and infection of the atopic eczema. Despite the authors conclusions there was insufficient evidence to recommend the combined treatment over the steroid alone treatment. [EL=2-] The funding of this study was undeclared.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						positive bacteria (Staph. and Strep.) were reduced from 80 to 15 with the combination treatment and 71 to 24 by steriod alone. Other bacteria were unaffected. Susceptability to fusidic acid was high with Staph. (MICs around 0.1ug/ml) and intermediate for Strep (MICs around 5ug/ml). Tolerance to treatments was similar in both groups.		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Goodyear HM;Watson PJ;Egan SA;Price EH;Kenny PA;Harper JI; 1993 Jul 420	Study Type: Case-control Evidence level: 2-	n=50 children with atopic eczema n=20 non-atopic control children	Children with atopic eczema (34% mild, 40% moderate, 20% severe, 3% very severe) aged 6 months to 14 years (mean age 4.4 years) None had had antibiotic therapy in the previous two months.	Intervention: none Comparison: Colonisation, phage typing and determination of resistance or sensitivity of the bacteria isolated from skin, nose, axillae and groin of children with atopic eczema compared to control non-atopic children.	Follow-up period: none Outcome Measures: Culture, identification and determination of resistance of bacteria (Contact agar discs by the Litsky method) from skin swabs	S.aureus was the most common pathogen isolated: 74% from worst eczema areas and 30% was unaffected areas in the group of children with atopic eczema, Carriage rates of S.aureus in the children with atopic eczema were 20% in the nose, 12% in the axillae and 18% in the groin compared with children in the control group from which 10% (2 children) grew S. aureus from nasal swabs but not from other sites. The most common S. aureus phage group was II (32%). 35% were not typeable. Resistance to penicillin was present in 88% of S.aureus strains. Resistance to 2 or more antibiotics occurred in 38% cases (sulphamethoxazole, erythromycin, trimethoprim,fusidic acid, mupirocin, gentamicin) No resistance to gentamycin , mupirocin or methicillin was detected.	This study confirms the role of S.aureus in atopic eczema in children and highlights the need to be prudent in the use and choice of antibiotics to treat atopic eczema.	A small study confirming previous data about S.aureus colonisation on the skin and nasal area of children with atopic eczema. The sensitivity and resistance data of the S .aureus are difficult to extrapolate due to the small number of children involved.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Goh CL;Wong JS;Giam YC; 1997 Sep 421	Study Type: Case-control Evidence level: 2-	n=33 patients with atopic eczema n=20 of unaffected patients	Patients presenting at an outpatient's clinic with atopic eczema Age range 3 months to 32 years (mean age 12.7 years) 13/33 (40%) were less than 10 years old Atopic eczema diagnosis: 52% mild 39% moderate 9% severe 79% were Chinese,185 were Malay and 35 Indian	Intervention: none Comparison: bacterial colonisation rates on eczematous and non-eczematous skin and nasal mucosa of children with atopic eczema and control children plus the bacterial resistance or sensitivity to antibiotics.	Follow-up period: none Outcome Measures: S. aureus colonisation and resistance/sensitivity to antibiotics.	46% of non-eczematous skin of children with atopic eczema was positive for S.aureus compared to 5% (one child) in the control group. 54% of nasal cutures were positive in atopic eczema children compared to 35% in the control group. 54% of cultures were positive for S.aureus from skin/nasal mucosae of children with atopic eczema compared to 20% in the control group. Results showed that S.aureus was very sensitive to cloxacillin, cephalexin,clindamycin and co-trimoxazole however 92.55 (49/53) of the S.aureus isolated from the atopic group was sensitive to erythromycin and 72.7% (24/53) of the S.aureus to tetracycline 13% of S.aureus was sensitive to penicillin and ampicillin in atopics and controls.	This study confirms that S.aureus colonisation is greater on the skin and nasal area of children with atopic eczema compared to controls and this is linked to the severity of the eczema. In this study, the S. aureus isolated was sensitive to most antibiotics but were generally resistant to penicillin and ampillicin .	A small study confirming previous data about S.aureus colonisation on the skin and nasal area of children with atopic eczema. The sensitivity and resistance data of the S .aureus are difficult to extrapolate due to the age of the study and the small number of children involved.
Shah M; 2003 May 422	Study Type: Case-control Evidence level: 2-	Study group: n=48 hospital dermatology outpatients of which 23 were atopic eczema patients Control groups: n=119 primary	Severity of atopic eczema was not recorded. The age range of the total study population was 6 months to 75 years (mean age 6.7 years)	Intervention: none Comparison: Rates of fusidic acid resistance in microbiology samples between dermatology patients seen overa 4 month	Follow-up period: none Outcome Measures: Resistance of microbiology samples to fusidic acid by culture and the modified Stokes disc diffusion method.			

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
		care n= 111 hospital inpatients n=71 non-dermatological outpatients		period and non-dermatology patients.	Prescribing details of fusidic acid prepations in the local PCT			
El-Zimaity D; Kearns AM; Dawson SJ; Price S; Harrison GAJ; 2004 424	Study Type: Other Evidence Level: 3	Intervention: none Comparison: none	n=2476 records of which there were clinical details of 2170, of these 7.3% were eczema. No individual data as to the number of paediatric patients in this group	Subjects had clinical records on clinical isolates of S.aureus from skin swabs.	Details on the patterns of fusidic acid resistance among S.aureus swabs in the Carmarthen area UK 1997-2001: Year Hospital department Details of isolates and their susceptibility to fusidic acid presented in age groups Total amount of prescriptions of fusidic acid preparations in hospital and GP setting. Phenotypic and genotypic characteristics of 31 strains of S.aureus	Between 1997-2001 there was a rise in fusidic acid resistance particularly among paediatric patients with atopic eczema and impetigo. No individual data for atopic eczema but fusidic acid resistance in the participants under 10 years of age were: 1997: 5.1% 1998: 4.3% 1999: 17.5% 2000: 14.6% 2000: 24.6% Total fusidic acid prescription between 1997 and 2001 were In hospital: 198 and 219 In 17 GP: 3375 and 5078 respectively. Clinical isolates from 2002 swabs showed that in vitro resistance was more likely to occur in samples from impetigo as opposed to eczema, dematitis and abscesses.	Study provides data on fusidic acid resistance in S.aureus isolates in the Carmarthen area UK which indicates there is an increase within paediatric patients with atopic eczema.	This survey shows an increased localised S.aureus resistance to fusidic acid preparations most likely connected with increased prescriptions. [EL=3] It is important to note that these observations can not be extrapolated to the UK in general and that each region need to be monitored individually.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Hanifin JM; Rogge JL; 1997 [373]	Study type: Case report Evidence level 3	n=1 A further 3 case reports were noted but not described in detail.	6 year old girl with a history of recurrent flares of atopic eczema from the age of 3 months and also severe asthma for the age of 5 years.	After several episodes of pyoderma which were treated with antibiotics she presented with severe exacerbation of her atopic eczema	Cultures from swabs of the infected areas revealed *S.aureus* which was resistant to erythromycin and a β-haemolytic Streptococcus	Over the following year , 7 separate courses of antibiotics were prescribed which overall were insufficient to control infection	
Hoeger P; Ganschow R; 2000 [374]	Study type: Case report Evidence level 3	n=2	Case 1: 22 month old boy with atopic eczema from the age of 4 weeks complicated with recurrent infection. Case 2: 4 year old girl with atopic eczema from 7 months of age complicated with recurrent infection.	Case 1: He was admitted to hospital with fever with increasing redness in his lower left leg. His skin was extremely dry with widespread excoriated papules and patches. Bacterial cellulitis was diagnosed. Case 2: she was admitted to hospital with a 5 day history of fever and vomiting since the previous night. Generalised atopic eczema was noted.	Case 1: Laboratory tests were indicative of an infection. Cultures from swabs of infected areas revealed S.aureus and infection resistant to penicillin, ampillicin. Case 2: Blood counts and cultures were indicative of S.aureus resistant to penicillin and ampicillin	Case 1: He was treated with iv. ampillicin and flucloxacillin in addition to topical crystal violet (0.3%) and 1% hydrocortisone ointment. He was discharged after 12 days. Case 2: She was treated with iv. flucoxacillin and tobramycin with topical therapy of crystal violet and hydrocortisone. She was discharged 25 days later but had a similar reoccurrence four weeks later.	Case 2: This child was of particular concern as she had a congenital ventricular septal defect which was monitored during both infections by echocardiography for signs of endocarditis. None were found.
Sharma AK; 1997 [375]	Study type: Case report Evidence level 3	n=1	4 year old boy with atopic eczema with cutaneous colonisation with S.aureus unresponsive to topical medication	Child was hospitalised due to deterioration in his condition. He was moderately pruritic, infiltrated, slightly scaly patches were apparent intermingled with excoriated papules of which some oozed a seropurulent	Serum IgG was mildly elevated and Serum IgE was moderately elevated. Other laboratory tests were within normal limits. Cultures of swabs grew *S.aureus* resistant to penicillin, tetracycline and co-trimoxazole	Child was given oral promethazine and a topical steroid-antibiotic cream for 3 weeks over which time, little improvement in the skin was seen and it was noticed that right leg below the knee was oedematous. Following x rays and	The improvement in the atopic eczema lasted for 5 years follow up.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
				discharge.		biopsy , chronic osteomyelitis was confirmed and the material excised grew S.aureus. This was treated with oral erythromycin and after 3 months the skin condition had improved and osteomyelitis was eliminated.	
Pike MG; Warner JO; 1989 [376]	Evidence level: Case report Evidence level 3	n=1	3.5 year old boy with severe atopic eczema with recurrent skin infections since infancy and also had asthma.	His treatment consisted of an exclusion diet, calcium supplements, mild topical steroids and emollients. Ketotifen and terbutaline for asthma. Asorbic acid and and cimetidine for defective chemotaxis and frequent oral and topical antibiotics for his skin infections. He was admitted to hospital with continuing skin sepsis in spite of treatment.	Following a history of murmur an echocardiogram confirmed a ventricular septal defect and blood cultures grew *S.aureus* leading to the diagnoses of acute bacterial endocarditis.	Surgery corrected his septal defect and he was treated with high dose steroids. He had two further episodes of septicaemia due to *Proteus mirabilis* and *Pseudomonas aeruginosa*	In long term follow up the boy continued to have severe atopic eczema subject to recurrent skin sepsis.
Adach J; Endo K; 1996 [380]	Study type: Case report Evidence level 3	n=2 of which one was a child.	5 year old girl with moderate atopic eczema since infancy.	Presented at clinic with skin eruptions on face and fore arms which had rapidly worsened in the past 2 days accompanied by slight fever	Infection with streptococcal impetigo was diagnosed and treated with oral ampicillin for 14 days. Microbial cuture detected Group G streptococci and S.aureus. A reoccurrence of the infection		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
					occurred 6 months later and was successfully treated in the same way.		
Scheinfeld N; 2003 [381]	Study type: Case report Evidence level 3	n=1	An infant of ~9 months who had had atopic eczema from ~one month old and an extensive history of antibiotic use both for his skin, ear and oral fungal infections.	In spite of a typical impetiginised atopic eczema appearance, skin cultures revealed the presence of Acinetobacter *spp.* (*A.lwoffi* and *A.anitratus*) resistant to β-lactam antibiotics	The impetiginised rash cleared with 4 days of i.v. cefotaximine, gentamicin and emollients.		Presence of unusual pathogens with atopic eczema are likely to be due to the extensive prior use of antibiotics.
Callen JP; 1983 [388]	Study type : Case report Evidence level 3	n=1	8 month old male with infantile atopic eczema being treated with emollients, hydrocortisone hydrochloride cream and oral diphenhydramine hydrochloride elixir	Infant was hospitalised with a generalised hyperpigmented lichenified rash with asteatosis and fever. Disseminated vesicles with central umbilication were noted on the skin mainly on the face and neck. The neck was rigid and there was bilateral conjunctivitis. Herpes simplex virus infection was confirmed by culture.	The child was treated with iv. vidarabine (adenosine arabinoside) because of presumed systematic involvement. The response was good.		Both mother (breast) and 8 year old sibling (around mouth) of the infant in the case report were diagnosed with eczema herpeticum and treated accordingly.
David TJ; Lakhani PK; 1984 [389]	Study type: Case report Evidence level 3	n=1	10 year old girl with atopic eczema from the age of ~3 months which developed into severe atopic eczema despite treatment with topical hydrocortisone and Synacthen Depot twice weekly. Constant bandaging of the hands was also used. All resulted in significant absence from school.	History of many infections: S.aureus Strep.spp Pseudomonas aeruginosa 3 attacks of pneumoncoccal meningitis and septicaemia Herpetic gingivostomatitis			This case report is extreme with the child missing 2 years of school and when eventually leaving an extensive hospital stay was rehabilitated in a school for physically handicapped children.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
				Eczema herpeticum Plus radiological evidence of rickets			
Cox GF; Levy ML; 1985 [390]	Study type: Case report Evidence level 3	n=1	10 year old female with a lifelong history of atopy manifested by mild eczema and moderate to severe asthma and rhinitis	5 days after having a 'whirlpool spa bath' with a friend with 'active fever blisters' on her lower lip she noted painful blisters on her hands which spread and she developed a fever. This was diagnosed as eczema herpeticum	On admission to hospital she was treated with i.v. piperacillin and systemic hydrocortisone and topical steroids with occlusion. Her condition deteriorated. iv. aciclovir was then used and the vesicles were dry within 5 days.		This article speculates that eczema herpeticum may be associated with the use of hot tubs.
Muelleman PJ; Doyle JA; 1986 [391]	Study type: Case report Evidence level 3	5.5 year old boy with atopic eczema and asthma	History of watering and mattery eyes and a rash in the groin for 5 days which was not responding to topical and oral steroids and antibiotics.	On examination the rash was identified as eczema herpeticum both around eyes and groin area which was confirmed by culture.	Oral aciclovir was prescribed and Polysporin ointment for the facial lesions. Lesions were healing within four days. A month later the infection reoccurred and was treated in the same way.		
Sanderson IR; Brueton LA; 1986 [392]	Study type: Case report Evidence level 3	1 year old boy with atopic eczema was managed with liquid paraffin/white soft paraffin (50:50), hydrocortisone ointment and regular baths with emollient and emulsifying ointment.	The boy had become lethargic and febrile and on admission had a fever and was covered with herpeticum eruptions. He was 10% dehydrated with sunken eyes, reduced skin turgor and cold extremities	Eczema herpeticum was diagnosed clinically immediately and by culture 4 days later.	Treatment included rehydration and iv. acyclovir and broad spectrum antibiotics Despite intensive treatment he suffered a cardiac arrest, spontaneous cutaneous and gastric bleeding and required i.v. feeding and ventilatory support. His skin was treated with potassium permanganate. He		This case study shows the seriousness of Eczema herpeticum if not diagnosed promptly. There was a lag time of one week between initial symptoms and diagnosis

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
					made a full recovery and was discharged after 4 weeks		
Bajoghli A; Babl FE; 1999 [393]	Study type: Case report Evidence level 3	15 month old boy with a history of atopic eczema since the age of 2 months and treated with topical corticosteroids and emollients.	Admitted to hospital due to exacerbation of his chronic atopic eczema with worsening pruritis, increasing weeping lesions, irritability and fever. He had just received his varicella vaccination and had been in contact with a visitor with cold sores 2 months earlier.	Eczema herpeticum was diagnosed by clinical examination, microscopic examination of facial erosions samples and finally bacterial skin and blood cultures.			
Katta R; 2001 [394]	Study type: Case report Evidence level 3	9 month old boy with a history of atopic dermatitis only partially controlled with emollients and mild topical steroids	The boy was admitted with a fever, worsening of eczema on one arm and increasing pain, redness and skin breakdown for 3 days.	Physical examination leads to the diagnosis of an eczema herpeticum on the left arm. Herpes simplex was subsequently confirmed by culture. Blood cultures grew *S.aureus*	Treatment was i.v. nafcillin sodium and acyclovir for 7 days after which the child recovered.		
Mackley CL; Adams DR; 2002 [395]	Study type: Case report Evidence level 3	6.5 month old female with a history of atopic eczema	Child was presented to GP with a foul smelling, sore rash on the face. It was treated with oral antibiotics and referred. On presentation to consultant, papules and vesicles were present on the face and a fever recorded. Eczema herpeticum was diagnosed.	Treatment was oral aciclovir and by 4 days the erosions were healing and the inflammation markedly decreased.			
Khan MS; Shaw L: 2005 [396]	Study type: Case report Evidence level 3	18 month old baby with a history of eczema	The child was presented at hospital with a fever and. malaise. On clinical examination, diffuse ulcers were seen in the mouth and an extraoral rash was observed. It was only after a second referral that the diagnosis of eczema herpeticum was made	Treatment was i.v. antiviral treatment and systematic antibiotics plus parenteral fluids and analgesics.			
Lipman BL; 1983	Study type: Case report	n=1	A male infant aged 30 months with a history of atopic eczema from 6 weeks	A generalised verrucae vulgares infection complicating			

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
[398]	Evidence level 3		of age treated with hydrocortisone, Cristo shortening and bath oil.	the atopic eczema was diagnosed at when the child was 12 months old.			
Solomon L; Telner P; 1966 [401]	Study level: Case report Evidence level 3	n=1	A 2.5 year old girl with a 12 month history of mild atopic eczema	Presented at clinic with asymptomatic popular lesions in the nappy area and lower limbs. Molluscum contagiosum was diagnosed clinically nad microscopic examination of a biopsy specimen	As new crops of papules continued to appear, the following treatments were tried: 1. the child was put under general anaesthesia and visible lesions were opened and Curetted. 2. carbon dioxide snow 3.electrodessication 4. simple rupture by mother It was finally cleared following treatment with oral methisazone (antivaccina virus agent) and topical 1% iodine.		It was commented on by the authors that the resolution of infection may have been due to the antiviral treatment or may have been the infection had run its natural course.
Keipert JA; 1971 [402]	Study level: Case report Evidence level 3	n=6	6 children (3 girls) aged 10 months to 7 years with atopic eczema of varying severity.	Children presented at clinic with molluscum contagiosum (no details of diagnosis) on various areas of the body e.g. thighs, upper arms, ears One child had developed atopic eczema after developing a molluscum infection	Treatments included: Salicylic acid and lactic acid, lesion incision, podophyllin and topical iodine,		
Block SH; 1972 [403]	Study level: Case report Evidence level 3	n=1	Four-year old girl with a history of eczema	Girl presented at clinic with molluscum contagiosum infection	No detail of treatment but it was noted that the child's atopic eczema was		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
					mostly on her arms and legs and the infection mainly on her trunk.		
Luber H; Amornsiripanitch S; 1988 [418]	Study level: Case report Evidence level 3	n=1	Four-year old boy with a history of atopic eczema who was chronically colonised with *S.aureus* that had become resistant to methicillin a year previously.	At 3.5 years he developed osteomyelitis of three fingers and *S aureus* (resistant to erythromycin, cephalexin and methicillin) was cultured	Treatment was i.v. vancomycin and topical mupirocin. His osteomyelitis recurred once but was successfully resolved with the same treatment.		This is an extremely rare type of case report

Stepped approach to management

Managing flares

Bibliographic Details	Study type and evidence level	No. of studies	Study Characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Langan SM;Thomas KS;Williams HC; 2006 425	Study Type: Systematic Review/Meta-Analysis Evidence Level: 1+	Total number of studies = 15	Studies that discussed 'flare'. (The eligibility criteria were not stated explicitly).	Definition of a flare	Definitions A change in severity score above a set threshold (change in SCORAD score of 50-80% or more than fifteen points; increase in TIS score of at least four points; COSTA score increased by 70%; or disease activity scores by more than 75%) – seven studies. The need to use topical corticosteroids (disease state requiring TCS for 3 days or more; need to use potent TCS of further systemic treatment; or investigator deemed that TCS were needed for 3 days or more – one study each). IGA score 4 or more, TCS used within 3 days of visit of her medical appointment and preceded by 7 days without TCS use - three studies. An IGA score of at least three with a score of two or three for any two signs or symptoms (erythema, itch, papulation, induration/oedema) – one study. A scratch score of more than two on a five-point scale for 3 consecutive days – one study.	

Bibliographic information	Study type and evidence level	Aim of study	Number of patients	Patient characteristics	Outcomes	Comments
Zuberbier T;Orlow SJ;Paller AS;Taieb A;Allen R;Hernanz-Hermosa JM;Ocampo-Candiani J;Cox M;Langeraar J;Simon JC; 2006 96	Study Type: Cross-sectional survey Evidence Level: 3	To consider the effects of AE on the lives of those affected, and how that varies with age, gender, and severity of disease; to ascertain how patients/carers manage the disease; and to determine how well patients believe that their AE is controlled.	Total No. of Patients = 2002	Adults, or carers of children with atopic eczema. 39% were carers of children aged 2-13 years, and 61% were aged older than 13 years. Overall 69% had moderate AE, and 32% severe. Exclusions: those not experiencing a flare of AE within the last 6 months (flare defined as a sudden worsening of symptoms requiring a physician consultation or application of prescription medication).	Disease characteristics during a flare (children aged 2-13 years) mean 8.7 flares per year mean duration of flare 14 days number of days per year in a flare 121.8 number of nights sleep affected during a flare 5 number of times woken up at night during a flare 1.8 86% avoid at least one everyday activity 30% stated flare affected school/work life 34% stated flare affected home life 27% stated affected social life percentage time at school/work performance affected during a flare 7% days absent from school/work because of a flare 2.0 Funding: Novartis Pharma AG Management of a flare overall (all ages): 65% used TCS prescribed by a physician to treat a flare (in 54% this was the main means of treating the flare) 4% used emollients to treat flares (27% used prescribed emollients overall) 25% used pimecrolimus to treat a flare (in 18% this was the main means of treating the flare) 9% used tacrolimus to treat a flare (in 6% this was the main means of treating the flare). [Any combinations used to treat flares were not reported]	Funding: Novartis Pharma AG
Ricci G;Patrizi A;Bendandi B;Menna G;Varotti E;Masi M;	Study Type: Cohort Study Evidence Level: 2-	To evaluate the effectiveness of a new silk fabric in the treatment of	Total No. of Patients = 46 Silk fabric* N = 31	Children aged 4 months to 10 years (mean 2 years) with atopic eczema, in a phase of exacerbation (not defined) at the time of examination.	Outcomes at 7 Days: SCORAD (mean score change) -13 (30%), p=0.003 vs baseline	Funding: none declared The investigator undertaking the assessments was blind to the intervention.

Bibliographic information	Study type and evidence level	Aim of study	Number of patients	Patient characteristics	Outcomes	Comments
2004 426		young children with atopic eczema affected by a flare.	Cotton clothing (continued to wear cotton clothing) N = 15		-1 (2%), p=0.886 vs baseline Local score** -42%, p=0.001 for covered area -16%, p=0.112 for uncovered area	*the silk fabric used was MICROAIR Dermasilk, which also has antibacterial properties due to an 'exclusive water-resistant' treatment with AEGIS AEM 5772/5, a durable antimicrobial finish for textile products (based on the compound alkoxysilane quaternary ammonium). Children were instructed to wear silk products all day long - they were provided with the following items according to cutaneous involvement: body suit for the trunk (n=6), rompers for the whole body (n=11), leggings for the lower limbs (n=5), tubular bandages for small parts of the arms and legs (n=6), gloves for the hands (n=2), waist bands for the lower abdominal area near the nappy (n=2). Emollients were used by all, but topical corticosteroids were not permitted. No between-group analysis was undertaken for the outcomes. All the 26% of the silk group who withdrew were excluded from the analysis. Other than the SCORAD scores no other baseline data were provided.

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Hanifin J;Gupta AK;Rajagopalan R; 2002 Sep 427	Study Type: Randomised Controlled Trial Evidence Level: 1+	Total number of patients = 348 Fluticasone propionate cream 0.05% N = 229 Vehicle N = 119	Children and adults, aged 3 months to 65 years (mean 16.8 years) with atopic eczema who had received treatment with fluticasone propionate cream 0.05% for up to 4 weeks, together with an emollient.* Approximately 75% had 'continuous atopic eczema without remission'. In 63% the atopic eczema was of moderate severity, and in 37% it was severe. Overall 66% were aged 2-17 years, and 32% were aged 5 years or below. In 18%, less than 9% of the skin was involved; in 45%, between 9% and 36% of the skin was involved, and in 32%, more than 36% of the skin was affected. Exclusions: eczema of only the face, feet or hands; erythroderma or toxicoderma, psoriasis, contact dermatitis at sites of AE, atrophy or telangiectasia, systemic treatment for AE within 1 month, topical treatment with tar or TCS within 1 week, or concomitant systemic or topical treatment with antibiotics or corticosteroids.	Fluticasone propionate cream 0.05%* vs Vehicle*	Outcomes at 20 Weeks: Relapse (% children) 27% vs 66% (p value not reported) vs OR of not having a relapse in fluticasone group 8.1 (95% CI 4.3 to 15.2), p<0.001 vs Median time to relapse (children) Could not be estimated for fluticasone because most were controlled at 20 weeks vs 5.1 weeks, p<0.001 vs Global assessment (children) 72% excellent or good vs 34% excellent or good vs Adverse effects 31% reported at least one vs Cosynotropin stimulation test (n=44) 'Evidence of possible adrenal suppression' in two (unclear whether children or adults): one with more than 35% BSA affected, intermittent FP use for 345 days (post	Source of Funding: GlaxoWellcome Inc *those whose condition had stabilised were randomised to continued use of FP cream 0.05% (intermittently), or to its vehicle base (stabilisation was defined as an IGA score of 2 or less [scale 0-5], and a score of 1 or less [scale 0-3] for each of erythema, pruritus, and papulation/excoriation. During stabilisation FP was used twice daily - for the first 4 weeks of the maintenance phase (this RCT), treatment was applied once daily four times a week (Sunday, Tuesday, Thursday, Saturday). For the remaining 16 weeks FP was applied once a day on 2 days of the week (Sunday and Thursday). Emollients were continued. A relapse was defined as an IGA score of 3 or more, and a score of 2-3 for any of the three signs/symptoms: erythema, pruritus, and papulation/induration/oedema. In children the median exposure to FP was 335 days.

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					stimulation test cortisol level 17mcg/dl - minimum level should be 18); one with post stimulation level 9 mcg/dl (BSA affected less than 35%).	
Berth-Jones J;Damstra RJ;Golsch S;Livden JK;Van HO;Allegra F;Parker CA;Multinational Study Group.; 2003 Jun 21 428	Study Type: Randomised Controlled Trial Evidence Level: 1+	Total number of patients = 376 Fluticasone propionate cream 0.05% N = 70 Vehicle (following stabilisation with FP cream 0.05%) N = 84 Fluticasone propionate ointment 0.005% N = 68 Vehicle (following stabilisation with FP ointment 0.005%) N = 73	Young people and adults aged 12-65 years (mean 28.8 years) with recurrent moderate to severe atopic eczema with a flare (score of 4 or more on TIS [sum of 3 signs; erythema, oedema or papulations, and excoriations, each 0-3]). Exclusions: medical conditions that would mean TCS were contraindicated; other dermatological conditions.	Fluticasone cream 0.05%* vs Vehicle (following stabilisation with FP cream 0.05%) vs Fluticasone propionate ointment 0.005% vs Vehicle (following stabilisation with FP ointment 0.005%)	Outcomes at 16 Weeks: Relapse (% with) 19% vs 64% vs 40% vs 56% vs Hazard ratio for remaining free of relapse 5.8 (95% CI 3.1 to 10.8), p<0.001 (cream vs vehicle) 1.9 (95% CI 1.2 to 3.2), p=0.01 (ointment vs vehicle) vs Median time to relapse >16 weeks vs 6.1 weeks vs >16 weeks vs 6.1 weeks vs Adverse effects	Source of Funding: GlaxoWellcome *Patients were randomised to the stabilisation and maintenance phases of the study at the outset - initially the flare was stabilised with FP cream 0.05% or ointment 0.005%, used once or twice daily for 4 weeks (4 treatment groups). Those in remission thereafter (TIS score of 1 or less for index lesion) used the same formulation of FP as during the stabilisation phase or its vehicle base - treatment was applied on 2 consecutive evenings of the week, for up to 16 weeks. Treatment was applied to all healed sites of potential relapse and any newly occurring sites. Patients also used emollients (a cetomacrogol-based cream) twice daily (or once daily on 'treatment days'), and used a bath oil as needed. Comparisons between FP cream and ointment during the stabilisation phase were also reported, as were differences between once and twice daily use - data not reproduced here.

Bibliographic Details	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Adverse event rates for all events not reported. During stabilisation: the most common events were ear, nose, and throat infection. 4 events classified as serious (erysipelas, exacerbation of asthma, 2 flares of eczema). Visual signs of atrophy in 3 patients - 2 using the FP ointment, and had telangiectasia and striae, one using the cream had telangiectasia (only 1 of the 3 was newly observed). During maintenance: no visual signs of skin changes or atrophy.	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Kirkup ME;Birchall NM;Weinberg EG;Helm K;Kennedy CT; 2003 Sep 255	Study Type: RCT Evidence level: 1+	Two multicentre RCTs in one report Exclusions: signs of skin infection; severe atopic eczema requiring hospital admission; treatment with very potent or systemic corticosteroids in the previous 3 weeks; history of adverse response to corticosteroids	Children experiencing a flare of moderate to severe atopic eczema (total atopic eczema score of 6 or more*), treated at outpatient clinics. Age 2-14 years, mean age 8 years Mean number of body areas affected, 67% (8 out of a possible 12)	Intervention: Study A: Fluticasone propionate 0.05% cream (n=70) Study B: Fluticasone propionate 0.05% cream (n=66) Acute phase - twice daily for 2-4 weeks until atopic eczema stabilised Maintenance phase - intermittently up to twice daily as required for 12 weeks plus emollients as required Comparison: Study A: Hydrocortisone cream 1% (n=67) Study B: Hydrocortisone 17-butyrate cream 0.1% (n=62) Acute phase - twice daily for 2-4 weeks until atopic eczema stabilised Maintenance phase - intermittently up to twice daily as required for 12 weeks plus emollients as required	Follow-up period: Duration of treatment, acute phase (2-4 weeks) and maintenance phase (up to 12 weeks) Outcome Measures: Study A 1) Total atopic eczema score* (reduction in scores, and mean difference between groups) 2) Patient's diary at end of acute phase (change in score vs baseline; difference in scores at endpoint. Score used was 1-7, worse than ever to better than ever) a) rash b) itch c) sleep disturbance 3) Physician's assessments: Improved=better than ever, or better than usual, Not improved= same, worse than ever, or worse than usual 4) Median time to recurrence during the maintenance phase (days) 5) Adverse effects 6) Withdrawals Study B 1) Total atopic eczema score* (reduction in scores, and mean difference between groups)	Study A (fluticasone vs HC 1%) 1a) At the end of the acute phase: -4.91 (41%) vs -2.37 (20%), difference -2.39, 95% CI -3.47 to -1.31, p<0.001 1b) At the end of the maintenance phase: -6.87 (57%) vs -4.84 (41%), difference -1.88, 95% CI -3.20 to -0.56 p=0.006 2a) +31% vs +8%, difference 0.81, 95% CI 0.45 to 1.16, p<0.001 2b) +29% vs +9%, difference 0.70, 95% CI 0.33 to 1.07, p<0.001 2c) +26% vs +12%, difference 0.46, 95% CI 0.08 to 0.84, p=0.019 3) 94% vs 85% improved, p=NS 4) 62 (range 7-118) vs 36 (7-114) 5) 29% vs 31% reported an adverse event 7% vs 10% general symptoms 8.5% vs 6% influenza 8.5% vs 8.5% 'miscellaneous events related to the skin' Possibly related to treatment: 1% vs 0% folliculitis and ringworm 0 vs 1% severe flare with secondary infection 6) 26% vs 20% reasons: 2.9% vs 12% treatment failure	Funding: Glaxo Wellcome R&D UK. Multicentre RCT. The two studies were identical in design. *Total atopic eczema score (Max, 21) = Number of body areas affected (out of possible 12 body areas) + sum of three signs (erythema, excoriation and lichenification) graded as 0-3 for target area (max 9) Recurrence of atopic eczema was defined as an increase of 1.0 in either the number of body areas affected or in the sum of scores for the target area. Use of regular inhaled or intranasal corticosteroids was permitted

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
					2) Patient's diary at end of acute phase (change in score vs baseline; difference in scores at endpoint. Score used was 1-7, worse than ever to better than ever) a) rash b) itch c) sleep disturbance 3) Physician's assessments: (same scale as above)	10% vs 3% non-compliance/personal 4.2% vs 1.5% early cure 0% vs 1.5% adverse event 11.4% vs 3% protocol violation/no reason Study B (fluticasone vs HC-17-butyrate 0.1%) 1a) At the end of the acute phase: -4.37 (41%) vs -4.52 (37%) difference -1.25, 95% CI -2.46 to -0.05, p=0.042 1b) At the end of the maintenance phase: -6.76 (63%) vs -6.78 (56%) difference -1.39, 95% CI -2.72 to -0.05 p=0.042 2a) +11% vs +10%, difference 0.38 95% CI -0.01 to 0.77, p=0.056 2b) +11% vs +12%, difference 0.50 95% CI 0.09 to 0.92 p=0.017 2c) +7% vs +7%, difference 0.48 95% CI 0.11 to 0.85, p=0.011 3) 98% vs 84% improved, p=0.024 4) 51 (range 7-121) vs 57 (9-123) 5) 42% vs 35% reported an adverse event 12% vs 8% upper respiratory tract infection 11% vs 2% cough 8% vs 15% 'miscellaneous events related to the skin' Possibly related to treatment: 1.5% (n=1) vs 0% red papules/boil 0 vs 3.2% (n=2) itchy skin after applying	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
						cream 0 vs 1.6% minor skin infections and pustules 0 vs 1.6% impetigo on the face 6) 11% vs 18% reasons: 0% vs 8% treatment failure 3% vs 4.8% non-compliance/personal 1.5% vs 4.8% adverse event 6% vs 9.7% protocol violation/no reason	

Phototherapy and systemic treatments

Bibliographic details	Study type and evidence level	No. of patients	Patient characteristics	Intervention & comparison	Outcome measures, follow-up and effect size	Comments
Berth-Jones J;Arkwright PD;Marasovic D;Savani N;Aldrifge CR;Leech SN;Morgan C;Clark SM;Ogilvie S;Chopra S;Harper JI;Smith CH;Rook GAW;Friedmann PS; 2006 [63] Country: UK and Croatia	Study Type: Randomised Controlled Trial Evidence Level: 1	Total number of patients = 166 Mycobacterium vaccae 1mg (given by a 0.1ml intradermal injection) N = 56 Mycobacterium vaccae 0.1mg (given by a 0.1ml intradermal injection) N = 58 Placebo (phosphate buffer solution), 0.1ml by intradermal injection N = 52	Children aged 5-16 years (mean 9 years) with atopic eczema and a SASSAD score of more than 20 (means across treatment groups 30-36). Exclusions: clinically infected eczema, history of a serious adverse drug reaction to any drug, treatment with any vaccine, drug or device for investigational use within 3 months.	Mycobacterium vaccae 1mg vs Mycobacterium vaccae 0.1mg vs Placebo	Adverse effects (not reported by treatment group) 32% eczema (13% believed to be treatment-related) 14% infected eczema 10% asthma 8% upper respiratory tract infection 19% injection-site reactions (induration and erythema) 0.6% (n=1) injection-site haematoma Outcomes at 12 weeks: Pruritus (on a 5-point scale) No significant differences between groups (no data shown) TCS use Sleep disturbance (on a 5-point scale) -26% SASSAD (mean score change) -25% SASSAD (mean score change) -24%, p=NS between groups Outcomes at 24 weeks: % body surface area affected -13% vs -12% vs -15%, p=NS between groups Patient's global assessment 65% much or slightly better vs 67% much or slightly better vs 65% much or slightly better CDLQI (score change)	Source of Funding: SR Pharma Use of usual treatment (not defined) was allowed (including TCS), but not topical or systemic immunomodulatory agents. [EL=1-] because only those who completed treatment were analysed.

Bibliographic details	Study type and evidence level	No. of patients	Patient characteristics	Intervention & comparison	Outcome measures, follow-up and effect size	Comments
					+4.8 vs +5.4 vs +5.5, p=NS between groups	
Harper JI; 2000 Jan [440]	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 43 Ciclosporin 5mg/kg/day (starting dose) for 12 weeks N = 21 Ciclosporin 5mg/kg/day (starting dose) for 1 year N = 19	Children aged 2-16 years (mean 10 years) with severe atopic eczema refractory to TCS therapy, and having no contraindications to ciclosporin. Exclusions: treatment with systemic corticosteroids, cytotoxic agents, or phototherapy within 2 weeks.	Ciclosporin for 12 weeks vs Ciclosporin for 1 year	Remission 17 of 19 in weeks 1-12, for mean 66 days. 16 of 17 following second treatment course for mean 177 days vs 15 of 16 in weeks 1-12. Three patients stopped treatment between months 9-11 and were still in remission at study end. Quality of life (CDLQI) No numerical data given; only statistical significance of changes from baseline notes. No between group comparisons. Outcomes at 1 Years: SASSAD (mean score change) -22 (42%) vs -28 (56%), p=NS Body surface area affected (% change) -26 (39%) vs -34 (49%), p=NS Outcomes at 3 Months: Treatment-related adverse effects 14% nausea 19% paraesthesia 10% hypertrichosis 10% swollen gums 10% headaches 5% rhinitis 10% upper respiratory tract infection 5% abdominal pain 10% folliculitis 5% hyperuricaemia 29% withdrew (10% due to adverse effects, 0% treatment failure, 10% protocol violation, 10% uncooperative with dose/dose schedule)	Treatment could be restarted in either arm if patients relapsed (defined as a score of 75% or more of the baseline value). Remission was defined as a 40% reduction in baseline severity score. TCS were permitted throughout the study. Three children randomised were excluded from analyses due to no or minimal post baseline assessments.

Bibliographic details	Study type and evidence level	No. of patients	Patient characteristics	Intervention & comparison	Outcome measures, follow-up and effect size	Comments
					No significant change in serum creatinine or blood pressure values from baseline in either group. SASSAD (mean score change) -24 (46%) vs -27 (54%), p=NS Body surface area affected (% change) -25 (37%) vs -30 (43%), p=NS	
Heddle RJ; 1984 [450]	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 27 Oral + nasal beclometasone dipropionate* N = 27 Placebo N = 27	Children aged 3-14 years (mean 6.5 years) with moderate to severe atopic eczema for at least 3 months and who failed to respond adequately to conventional treatment with emollients, weak TCS (not specified), and systemic antihistamines. Twenty-four underwent prick testing to 6 allergens; all developed immediate weals of 2mm or more, and positive IgE levels to grass, house dust mite, cat dander, egg and cow's milk. None were receiving systemic or inhaled corticosteroids. Mean severity scores at entry** were 25 for redness, 26 for surface damage, and 19 for lichenification. In addition, 17 had a history of recurrent wheeze, 14 a history of recurrent rhinitis, or cutaneous wealing.	Oral + nasal beclometasone dipropionate* four times daily vs Placebo (double-dummy)	Outcomes at 4 Weeks: Redness (mean score change) -6.3 (25%) vs -1 (4%), p<0.02 Surface damage (mean score change) -6.5 (25%) vs +0.7 (2.7%), p<0.01 Lichenification (mean score change) 2.8 vs 3.5, p<0.05 Sleep loss (mean score) 2.2 vs 2.4, p>0.1 Daily antihistamine dose*** 0.71 vs 0.95, p<0.05 Daily TCS dose*** 0.99 vs 0.95, p>0.1 Parental global assessment (mean score) -0.8 vs -0.2, p<0.05 (significant treatment order interaction for this outcome, p<0.05) Adverse effects 0 (11% had skin infections) vs 0 (19% had skin infections)	Source of Funding: None declared; Glaxo supplied study medications [EL=1-] because baseline data were not complete, therefore it is not possible to tell whether groups were similar in all aspects other than the intervention. This was a double-blind, cross-over study, consisting of 2x4-week treatment periods with a 4-week washout period in between. *oral dose = contents of a 200microgram capsule of Becotide rotacaps suspended in about 20ml water; each nasal dose given as a single metered dose (50microgram) from a Beconase aerosol via each nostril (total daily dose 120mcg beclometasone dipropionate). Topical treatments and oral antihistamines permitted during the trial (89% were using a TCS). 'Some' children had been using empirical elimination diets which were continued (no further details). **severity assessment: skin divided into 20 areas, each scored on scale 0-3 for redness, surface damage,

Bibliographic details	Study type and evidence level	No. of patients	Patient characteristics	Intervention & comparison	Outcome measures, follow-up and effect size	Comments
						and lichenification. Daytime itch and sleep disturbance scored on 0-10 VAS. Global change in severity (parental assessment): -2 very much better, -1 somewhat better, o=no change, +1 somewhat worse, +2 very much worse. ***stated to be measured in 'inches'. No explanation, and also assumed that daily dose means quantity used.
Hanifin JM; 1993 Feb 458	Study Type: Randomised Controlled Trial Evidence Level: 1+	Total number of patients = 83 Interferon gamma 50 microgram per square metre per day by subcutaneous injection N = 40 Placebo N = 43	Children and adults aged 2-65 years with severe atopic eczema. Mean age 37 years in the interferon group, 28 years in the placebo group, p=0.01. 25% were aged 3-20 years (6 in the interferon group, 15 in the placebo group). Total severity score* 12. Body surface area affected 59%. Total serum IgE (IU/ml) 4475 in the interferon group and 3888 in the placebo group, p=0.94. Duration of disease 30.4 vs 21.7 years in the interferon and placebo groups respectively. 2% were taking prednisone for asthma, and 8% were taking systemic corticosteroids (unspecified) for atopic eczema.	Interferon gamma vs Placebo	Outcomes at 12 Weeks: 50% global improvement 45% investigator assessment 53% patient assessment (67% in 3-20 years age group) vs 21% investigator assessment, p=0.016 21% patient assessment, p=0.002 (67% in 3-20 years age group, p value not stated) Severity parameters 34.6% improvement (erythema) no numerical data for pruritus induration excoriations dryness lichenification Severity parameters 19.5% improvement (erythema), p=0.035 no numerical data for pruritus, p=0.11 induration, p=0.27 excoriations, p=0.045 dryness, p=0.54 lichenification, p=0.09 lichenification	Source of Funding: Genentech Inc *severity: 6 parameters (erythema, oedema/papulation/induration, pruritus, excoriations/erosions, scaling/dryness, lichenification) measured on a 0-3 scale, none-severe, maximum score 18. Patients (or presumably carers in the case of children) administered injections themselves. Paracetamol was taken 1 hour pre and 4 hours post dose. TCSs (triamcinolone acetonide 0.1% or HC 1% cream or ointment) were permitted. 6% withdrew, and 10% had the dosage reduced. Antibiotic and antihistamine use did not differ between groups (no data reported). Eosinophil, granulocyte counts also reported (not reproduced here). Logistic regression analysis was

Bibliographic details	Study type and evidence level	No. of patients	Patient characteristics	Intervention & comparison	Outcome measures, follow-up and effect size	Comments
					TCS use 24.89 ounces per square m vs 34.3 ounces per square m, p=NS (where TCS = triamcinolone acetonide 0.1% Adverse effects 60% headaches 30% myalgia, chills 12.5% transient granulocytopenia 16.3% mild transient increases in liver transaminase levels vs 28% headaches, p=0.004 % myalgia, chills not stated 2.5% transient granulocytopenia 2% mild transient increases in liver transaminase level	used to account for differences in baseline demographics.

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
Berth-Jones J;Finlay AY;Zaki I;Tan B;Goodyear H;Lewis-Jones S;Cork MJ;Bleehen SS;Salek MS;Allen BR;Smith S;Graham-Brown RA; 1996 Jun 64	Study Type: Case series Evidence Level: 3	To assess response to ciclosporin in children with severe atopic eczema.	Total No. of Patients = 27 Ciclosporin (capsules or oral solution) 5mg/kg/day (taken in two divided doses) N = 27	Children aged 2-16 years (mean 9 years) with severe atopic eczema refractory to TCS. At enrolment they were free of any uncontrolled infection, and had normal blood pressure, renal and hepatic function.	Severity (SASSAD) No numerical data, p<0.001 vs baseline Body surface area affected No numerical data, p<0.001 vs baseline Pruritus No numerical data, p<0.002 vs baseline Sleep disturbance No numerical data, p<0.005 vs baseline Irritability No numerical data, p<0.001 vs baseline for parental assessment; p<).06 for child's assessment Quality of life No numerical data, p<0.05 vs baseline. Scale used unknown TCS requirement No numerical data, p<0.001 vs baseline Global assessment of response Child/parental assessment: 8 no/minimal symptoms 13 considerable improvement 3 slight improvement 2 no/minimal change Corresponding investigator's ratings: 8, 14, 3, 1	Source of Funding: None declared Comments: TCS treatment was continued as required during the study. Antihistamines (continued use of) were the only systemic drugs the patients could use. The 2 withdrawals were due to: pharyngitis and an asthma attack (1) and adverse effects (1; nausea, headaches, paraesthesia). Pruritus, sleep disturbance, irritability and TCS requirement were measured on a 100mm VAS. All results were only shown in graphs.

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
					Global assessment of tolerability Child/parental assessment: 16 very good 8 good 1 moderate 0 poor 1 very poor Corresponding investigator's ratings: 21, 4, 0, 1, 0 Follow-up 2 weeks after treatment stopped In 11 of 20 assessed the total sign scores had not exceeded 75% of the baseline value; the scores were maintained for 6 weeks in 6, and were maintained for 6 months in 3. Adverse effects 26% headaches 22% abdominal pain 15% nausea 7% paraesthesia 7% tremor 7% upper respiratory tract infection 4% (n=1) loose stool 4% green stool 4% acid reflux 4% migraine 4% asthma exacerbation 4% pustules 4% hyperactivity 4% frequent micturition 4% facial swelling 4% sunburn	

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
					No statistical or clinical change in serum creatinine or blood pressure. 1 case of transient increase in serum bilirubin from 25-56 micromol/l at 4 weeks (treatment was continued, and the level fell to 23 micromol/l at 6 weeks).	
Bunikowski R;Staab D;Kussebi F;Brautigam M;Weidinger G;Renz H;Wahn U; 2001 Aug 442	Study Type: Case series Evidence Level: 3	To investigate the effects of ciclosporin with respect to clinical and immunological outcomes in children with severe atopic eczema.	Total No. of Patients = 10 Ciclosporin 2.5mg/kg/day (microemulsion) N = 10	Children aged 22-189 months (median 106) with severe atopic eczema (SCORAD 58-97, mean 74). Exclusions: systemic corticosteroids within 2 weeks, biochemical parameters above upper limit of normal, hyperkalaemia, hypertension, uncontrolled infection, malignancy (or history of), food allergy as a cause of atopic eczema.	Severity (mean change in SCORAD score) Reduction of at least 35% in 9 children (reduction 32% in 1); 7 of the 9 did not relapse during following treatment discontinuation (weeks 8-12) Adverse effects 0 hypertension. no significant changes in serum creatinine (1 transient increase that normalised - treatment was not discontinued). significant increase in bilirubin, p<).05, from 10-3-12.8 micromol/l. tolerability 'good or excellent' in 9 (patient assessment) and 8 (investigator's assessment)	Source of Funding: None declared Comments: The daily ciclosporin dose could be increased to a maximum of 5mg/kg/day, based on response; three received 5mg/kg, three 3.5mg/kg, and four 2.5mg/kg. Treatment was for 8 weeks followed by a 4-week period of follow-up. TCS therapy continued unchanged during the study. Relapse was defined as a SCORAD score of more than 80% of the baseline score. Immunological data were also collected and compared to data from 20 non-atopic healthy controls (aged 55-210 months, median 166 months). These data were interleukin and tumour necrosis factor alpha production by peripheral blood mononuclear cells. No numerical data were reported - interleukin levels were shown in graphs in an associated publication.[444] The quality of life of mothers was reported in an associated publication.[443]
Bunikowski R; 2003 Feb 445	Study Type: Case series Evidence Level: 3	To investigate the effects of ciclosporin on S. aureus colonisation in severe atopic eczema.	Total No. of Patients = 11 Ciclosporin 2.5-5.0 mg/kg/day N = 11	Children aged 22-197 months with severe atopic eczema refractory to TCS therapy. SCORAD index more than 50, and mean objective score more than 40 on two measurements separated by an interval of		Source of Funding: None declared Comments: Treatment was given for 8 weeks. Topical betametasone 0.01% to 0.05% was used twice daily.

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
				at least 2 weeks. All were 'heavily colonised' with S. aureus, and six required antimicrobial treatment for suppurative superficial S. aureus skin infection.		
Zaki I; 1996 Sep 441	Study Type: Case series Evidence Level: 3	To report the author's experience of using oral ciclosporin to treat children with severe atopic eczema.	Total No. of Patients = 18 Ciclosporin orally (initial dose 5-6mg/kg, adjusted according to response) N = 18	Children aged 3-16 years (mean 8.1 years) with severe atopic eczema sufficiently severe to warrant systemic therapy refractory to other forms of treatment (not specified).	Response (not defined) 8 excellent 8 good 1 moderate 1 poor Relapse interval Median 6 weeks (0-38) Adverse effects 1 nausea 'no significant change' in serum creatinine or blood pressure'	Source of Funding: None declared Comments: The median duration of treatment was 6 weeks (range 4-12). 4 of the children were also included in the Berth-Jones study.[64] Emollients were continued, but TCS discouraged during the study. Relapse was defined as the need to use potent TCS or to receive further systemic treatment.
Bourke JF; 1996 Apr 447	Study Type: Case series Evidence Level: 3	To document the success of ciclosporin treatment after switching brands.	Total No. of Patients = 1 Ciclosporin (formulation changed to microemulsion) N = 1	A 2.5 year old child with severe extensive atopic eczema unresponsive to potent TCS (no details) and intolerant to ultraviolet therapy, who was treated with ciclosporin 5mg/kg (brand: Sandimmum) for 6 weeks, during which the condition deteriorated. The treatment was changed to a different brand (Neoral) at the same dose.	Severity* (mean score change) severity -55% itching -38% sleep +47% irritability -37% Adverse effects No significant change in blood pressure, urea, creatinine, or electrolytes'. No further details.	Source of Funding: Sandoz provided Neoral Comments: Oral Sandimmum is no longer available in the UK. *Severity of six signs/symptoms, all graded on a scale of 0-3. Mother scored itching, sleep, irritability. The publication also details two other cases (both adults) with similar outcomes.
Murphy LA; 2002 Aug 454	Study Type: Case series Evidence Level: 3	To describe the experience of using azathioprine in children who had thiopurine methyltransferase genotyping over a 3-year	Total No. of Patients = 48 Azathioprine 2.0-3.5mg/kg/day (taken as a single dose) N = 48	Children aged 6-16 years (mean 6.9 years)* with severe atopic eczema, and thiopurine methyltransferase levels within the normal range.	Global response (parental assessment) 28 excellent (at least 90% response) 13 good (60-90%) 7 inadequate (less than 60%	Source of Funding: None declared Comments: Thiopurine methyltransferase (TPMT) activity is believed to be valuable in identifying individuals who are deficient in this enzyme, which leads to

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
		period.		Fifteen had previously been treated with systemic prednisolone, which was continued while azathioprine treatment started, and in a further 8, prednisolone was given at the same time as azathioprine. Five were previously treated with oral psoralen phototherapy, and three with ciclosporin.	response) Adverse effects 2% (n=1) eczema herpeticum 2% nausea, vomiting, diarrhoea 2% urticaria, vomiting (believed to be a hypersensitivity reaction) 31% transient lymphopenia 10% transient abnormalities in liver function tests 2% transient and 'mild' thrombocytopenia 0 neutropenia	impaired metabolism of azathioprine, and consequently may be at higher risk of developing myelosuppression. TPMT levels were taken in 91 children of which 76 were within the normal range. *of 91 who had the TPMT assay. The age of those treated at the time of treatment was 38-198 months (3.2-16.5 years), mean approximately 91 months (7.6 years). The total duration of treatment was 983 months in the whole group but the range and mean/median duration of treatment and/or follow-up was not quoted. The study was a retrospective review of case notes, and other sources of data/information.
Ahmed I; 2002 Jul 448	Study Type: Case report Evidence Level: 3	To document the reduction in raised blood pressure in one child following ciclosporin treatment.	Total No. of Patients = 1 Ciclosporin (5mg/kg/day initially, reduced to 4mg/kg/day after 4 months) N = 1	A 6-year old boy with high blood pressure (day 135/85, night 137/81, 24-hr 136/83mmHg) and severe atopic eczema treated successfully with ciclosporin. Corresponding heart rate 129, 126, 128. Had previously missed school regularly. Also had asthma and hayfever. Previous treatment: HC butyrate 0.1% with chlorquinaldol 3%, applied twice daily on limbs and trunks, and HC ointment 1% to face. Tubular bandages and emollients were used as a body suit. Budesonide inhaler was used for asthma, and 'occasional' oral prednisolone.	Change in blood pressure Follow-up period not stated; 'during treatment' blood pressure fell to: day 110/66, night 103/53, 24-hr 108/62. Corresponding heart rates 89, 80, 86	Source of Funding: None declared Comments: The child was admitted to hospital for ciclosporin treatment. The authors concluded that the raised baseline BP may have been due to stress or sleep deprivation related to atopic eczema; or previous treatment (topical corticosteroids).
Galli E;	Study Type:	To evaluate the role of a	Total No. of Patients = 7	Children aged 3-14 years	Severity score	Source of Funding: Ministero della Pubblica

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
1994 451	Case series Evidence Level: 3	bolus dose of intravenous methylprednisolone in the management of severe atopic eczema in children.	Intravenous methylprednisolone (20mg/kg/day for 3 days) N = 7	(mean 9 years and 7 months) with severe atopic eczema and chronic itching. Two had respiratory, symptoms (1 asthma, 1 chronic rhinitis). All had been treated with long-term standard therapy without significant improvement in symptoms. All had high IgE levels (total serum 2145 KU/l). Mean baseline severity score 49.	Less than 8 in 5 of 7 children (believed to be measured immediately after the 3-day treatment period). 'mild improvement' in the other 2 (score 30-40 for 'a few days')	Istruzione (40-60%) Comments: Clinical severity score: scale of 0-3 (none-severe) assigned to each of five features of atopic eczema (erythema, vesicles, 'fissuration', lichenification, itching). A 'dramatic' decrease in itching was also reported (no further details). Lymphocyte counts, CD4, IgG, IgA and IgM levels were also reported - data not reproduced here. IgE levels were reported to be 'unaffected' by therapy.
Sonenthal KR; 1993 May 452	Study Type: Case report Evidence Level: 3	To describe the use of a systemic corticosteroid for severe atopic eczema.	Total No. of Patients = 1 Prednisone 5mg daily N = 1	A 7-year old girl with a history of atopic eczema since age 1 year and asthma since age 3 years. Previous treatment TCS, tar baths, emulsions (not defined), oatmeal baths, and urea cream without success, and had multiple tapered corticosteroid doses (not stated whether systemic or topical). Rarely sleeps through the night due to pain and itching, and missed 45 days of school in the previous year. On presentation had lichenified, excoriated, erythematous skin. Skin tests positive to grass and dust mite, but not to milk, soy, peanuts, egg white or yolk, fish or wheat.	Response Follow-up period not specified. The child had an exacerbation of her skin disease while receiving prednisone 2.5mg once daily; the patient was 'stable' with a treatment regimen of prednisone 5mg once daily, triamcinolone cream 0.1% applied to her body, hydroxyzine and urea cream. 'She is much more outgoing, able to sleep through the night, and easier for her parents to manage'	Source of Funding: None declared Comments: No further details were given. Two other cases were described in this paper (both adults, aged 22 and 24 years).
van Meurs;	Study Type:	To report the occurrence of raised alkaline	Total No. of Patients = 2	Two case reports of children (both aged 2	Alkaline phosphase levels	Source of Funding: None declared

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
1998 449	Case reports Evidence Level: 3	phosphatase enzymes in children treated with ciclosporin.	Ciclosporin 5mg/kg (initial dose) N = 2	years) who were treated with ciclosporin for their atopic eczema and who both had elevations in plasma alkaline phosphatase levels	2-year old girl (treated for 6 weeks, followed up to week 8): 188, 1730, 2026, 2161, 1182 weeks 0, 4, 5, 7, 8 respectively 2-year old boy (treated for 12 weeks, followed up to week 30): 166, 176, 169, 170, 1927, 2177, 296, 156 weeks 0, 4, 8, 10, 12, 14, 16, 30 respectively	Comments: The authors note that the mother of one child was of Chinese descent, and the other was of Taiwanese origin; they also noted that they had not seen such changes in liver enzyme levels in other children treated (although the ethnic origin was not described).
Murphy LA; 2003 Nov 455	Study Type: Case reports Evidence Level: 3	To describe the use of azathioprine to treat refractory atopic eczema in children with lower than normal levels of thiopurine methyltransferase.	Total No. of Patients = 2 Azathioprine N = 2	Two children with refractory atopic eczema and thiopurine methyltransferase levels lower than the normal range who were treated with azathioprine. The 14-year old was treated with 1.25mg/kg/day for 10 months. The 7-year old was treated with 1mg/kg/day for 8 months	Global response (not defined) n 7 year old: greater than 90% improvement in signs and symptoms. Oral corticosteroid withdrawn during this time. In 14 year old: 'almost completely clear'. Oral corticosteroid withdrawn during this time. Adverse effects In 7 year old: varicella zoster virus, treated with oral aciclovir and antibiotics; the illness was no more severe nor protracted than would otherwise have been expected.	Source of Funding: None declared Comments: The normal range for thiopurine methyltransferase is 8-14.5nmol/hr/ml red blood cells. The levels in the 7- and 14-year olds were 5.5 and 4.8 respectively.
Forte WC; 2005 Nov 453	Study Type: Case reports Evidence Level: 3	To document a rebound effect on withdrawing systemic corticosteroid therapy	Total No. of Patients = 2 Systemic corticosteroid (no details) N = 2	Children aged 6 and 8 years treated with a systemic corticosteroid (the drugs were not specified).	Withdrawal effects (6-year old) Oral corticosteroid taken for 15 days, when dose reduced to 0.5mg/kg/day there was worsening of his condition - generalised erythematous bullosum lesions. Treated with antihistamines, weak TCS, skin hydration, 'environmental hygiene' - his condition improved. Withdrawal effects (8-year old) Used oral corticosteroid 'several	Source of Funding: None declared Comments: No further details given.

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
					times' during several periods of 15 days, always reporting worsening of the condition on treatment withdrawal (increase in size of the affected area, and exudation of the lesions). Resolved after 20 days without the systemic corticosteroid therapy.	
Noh GW; 1998 Dec 461	Study Type: Case series Evidence Level: 3	To evaluate immunological parameters as predictors of response to interferon gamma.	Total No. of Patients = 68 Interferon gamma 2x1,000,000 IU/square meters for 5 days (week 1), three times a week (weeks 2-4), then twice a week (weeks 5-6). N = 68	Children and adults (age range not reported) with severe atopic eczema of at least 12 months' duration, with an inadequate response to topical corticosteroids and antihistamines.	Severity (Costa's SSS) More than 20% (mean 63%) reduction in 34% Less than 20% (mean 8%) in 44% No response in the remainder (22%)	
Pung YH; 1993 Sep 462	Study Type: Case reports Evidence Level: 3	To describe the use of interferon gamma in two children with severe atopic eczema.	Total No. of Patients = 2 Interferon gamma 0.05mg/square metre three times a week N = 2	A 2-year old boy with severe atopic eczema which had not responded to potent topical corticosteroids. He also had asthma. A 5-year old boy with hyper IgE syndrome, and atopic eczema.	Response n 2-year old, initial improvement but flare in the 4th week. Interferon gamma dose doubled, but no response, therefore treatment was changed to interferon alpha. Total body surface area affected fell from 70% to 10% at week 16. In the 5-year old, severity score fell from 11 to 3; IgE from 21,000 to 8,500 IU/ml.	
Schneider LC; 1998 Mar 460	Study Type: Case series Evidence Level: 3	To evaluate the effectiveness and safety of interferon gamma for atopic eczema	Total No. of Patients = 15 Interferon gamma 50 micrograms by subcutaneous injection every day or every other day N = 15	Children and adults aged 3.6-57 years, (60% aged under 16 years) with severe atopic eczema.	Total body surface area -70%, p<0.001 Total clinical severity -45%, p<0.001 Adverse effects Treatment-related adverse effects: 47% headaches 13% fever 6.7% chills	Source of Funding: Genentech Inc Comments: Minimum duration of treatment was 22 months (range 22-76, median 36 months) The dose was 50 microgram/m2 daily for 12 months, reduced to every other day thereafter if less than 10% of body surface area was affected on two consecutive visits. Treatment was discontinued if less than 10% of body surface area was affected on two consecutive visits on the alternate day regimen.

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
						Severity of six signs/symptoms were scored on a scale of 0-3. Growth charts were used to monitor the patients aged under 16 years, which did not appear to show any effects on growth during the study.
Stevens SR; 1998 Jul [459]	Study Type: Case series Evidence Level: 3	To describe the outcomes of longer-term treatment with interferon gamma in patients with atopic eczema following participation in a RCT of the same treatment.	Total No. of Patients = 24 Interferon gamma 50 microgram per square metre by subcutaneous injection daily N = 24	Children and adults included in the Hanifin 1993[458] RCT. Age range 11-57 years (mean 36 years).	Total body surface area -63.7%, p<0.001 -40.2%, p<0.001 Global assessment 1.7 of possible 3, p<0.001 1.3 of possible 3, p<0.001 Total clinical severity -40.3%, p<0.001 -42.6%, p<0.001 Individual severity parameters All improved, p<0.001 (erythema, oedema, pruritus, excoriations, dryness, lichenification) All improved, p<0.05 Associated atopic symptoms -60% severity of allergic conjunctivitis, p<0.001 -58% severity of allergic rhinitis, p<0.005 -20.8% asthma, p=NS No numerical data for allergic conjunctivitis or rhinitis; p<0.01. -77% asthma, p=NS Adverse effects Increases in the liver enzymes aspartate aminotransferase and alanine aminotransferase at 1 year, which fell towards baseline at year 2.	Source of Funding: Genentech Inc Comments: Twenty-four patients were treated with interferon gamma for 1 year, and 16 for 2 years. Reasons for discontinuation between years 1 and 2 were inconvenience and nonadherence (2 each), and improvement without therapy, ineffectiveness, flulike symptoms, and unknown reasons (1 each). The severity of each sign/symptoms was assessed on a scale of 0-3.

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
					Serum creatinine was mildly elevated at year 2 but remained within the normal range. 16% 'transaminitis' 8% headache 8% malaise 8% acne vulgaris 8% neutropenia 8% arthralgias 4% (n=1) fever/chills 4% gastric and oesophageal ulcers 4% splenomegaly 4% herpes zoster 4% molluscum contagiosum 4% respiratory 'congestion' 4% theophylline toxicity 4% postherpetic neuralgia	
Horneff G; 1994 May 463	Study Type: Case reports Evidence Level: 3	To document the effects of interferon gamma in two children with severe atopic eczema	Total No. of Patients = 2 Interferon gamma by subcutaneous injection (50micrograms three times a week for 3 weeks, then 25micrograms three times a week for 1 week) N = 2	Two children with severe atopic eczema, which had not been treated successfully with standard treatment (a 4-year old boy and a 5-year old girl).	Response in 4-year old Reduction in body surface area affected from 11% to 4%. No significant change in parents' opinion. Remission lasted for 5 months. Response in 5-year old No response to the first course of treatment. After the second course (following a 2-week interval): Change in body surface area affected from 41% to 63%.	Source of Funding: none declared Comments: Where 'standard treatment' included TCS and allergen avoidance.
von Ruden U; 2002 443	Study Type: Case series Evidence Level: 3	To report the quality of life of mothers of children treated with ciclosporin.	Total No. of Patients = 10 Ciclosporin 2.5mg/kg N = 10	As for Bunikowski 2001.[442] (Children aged 22-189 months with severe atopic eczema).	Quality of life (FEN*) Change in the five subscales: -0.34 (11%) psychosomatic wellbeing, p=0.046 -0.02 (0.5%) satisfaction with medical treatment, p=NS -0.27 (8.6%) effects on social life,	Source of Funding: None declared Comments: The 8-week treatment period was followed by an additional 4-week follow-up period. *the five subscales are psychosomatic wellbeing,

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
					p=NS -0.45 (14.3%) emotional coping, p=0.027 -0.05 (1.4%) acceptance of the disease, p=NS	satisfaction with medical treatment, effects on social life, emotional coping, acceptance of the disease.
Patel L; 1996 464	Study Type: Narrative review/case reports Evidence Level: 3	To describe the use of interferon gamma as 'a last resort' in children with atopic eczema.	Total No. of Patients = 10 Interferon gamma (no dosage information) N = 10	Children with severe atopic eczema who had failed to respond to standard treatment. Ages at time of treatment: 10 years in one, uncertain in the remainder (age of onset from 2 months). All treated initially as hospital inpatients.		Source of Funding: None declared. Comments: No outcomes data were reported.
Leonardi S; 2004 Apr 446	Study Type: Case reports Evidence Level: 3	To document the use of ciclosporin in children.	Total No. of Patients = 3 Ciclosporin 5mg/kg/day (in two divided doses) N = 3	Children who had been treated with ciclosporin. The children were aged 2, 4, and 5 years, in whom conventional treatment had failed. All were hospitalised at some time, but it was unclear whether this was when ciclosporin treatment was initiated. In the 4-year old ciclosporin treatment was started at the age of 18 months.	Severity* In the 2-year old the score changed from 495-290; because not 'completely improved', antihistamines and emollients were used after ciclosporin was stopped, and 'satisfactory control' achieved. In the 4-year old the score changed from 312-142. Relapse occurred after 12 months, when another course of ciclosporin treatment was given for 4 weeks, at 3mg/kg/day. Remission lasted 7 months. No further details. In the 5-year old the score changed from 408-153. Sleep pattern improved. Relapse occurred after 4 weeks (score increased to 206), which was treated with emollients, TCS and antihistamines.	Source of Funding: None declared Comments: Serum ciclosporin levels also measured. *Score calculated using the 'rule of nines'; 20 body areas assessed for seven manifestations (pruritus, erythema, vesciculation, papules, excoriation, scaly crust, lichenification) scored on a scale of 1-4, none-severe. Therefore 140 (1x7x20) = 'normal'/baseline.
Bunikowski R; 2001 Aug	Study Type: Case series	See Bunikowski 2001[442]	Total No. of Patients = 30	This is a separate publication of the Bunikowski 2001[442] paper. No further details were		

Bibliographic details	Study type and evidence level	Aim of study	No. of patients	Patient characteristics	Outcomes and results	Comments
444				reported in this publication.		
Weatherhead SC;Wahie S;Reynolds NJ;Meggitt SJ; 2007 Feb 457	Study Type: Case series Evidence Level: 3	To conduct a dose-ranging trial of methotrexate for the treament of moderate-severe atopic eczema.	Total No. of Patients = 12 Methotrexate once weekly (starting dose 5mg, increasing to 10mg weeks 2-4, then by a further 2.5mg every week up to 22.5mg weekly [maximum]) N = 12	Adults aged 18 years and over with moderate-severe atopic eczema who had tried at least one second-line treatment (not defined) and whose condition was refractory to optimal emollient and TCS therapy. Exclusions: treatment with systemic immunosuppressants, phototherapy, sun-bed treatment, or herbal medicines within 3 months. Use of potent TCS within 2 weeks or topical calcineurin inhibitors within 4 weeks.		Source of Funding: None declared Comments: Usual treatment with emollients and TCS was continued. The median dose used to achieve control (marked improvement or more than 50% reduction in SASSAD score) was 15mg weekly.
Goujon C;Berard F;Dahel K;Guillot I;Hennino A;Nosbaum A;Saad N;Nicolas JF; 2006 456	Study Type: Case series Evidence Level: 3	To report the use of methotrexate for the treatment of atopic eczema.	Total No. of Patients = 20 Methotrexate once weekly (25mg intramuscular in 14, oral does [7.5mg-25mg] in 6) N = 20	Adults aged 17-68 years with moderate to severe atopic eczema, who had insufficient response to 'routine' treatment or with an affected body surface area too extensive for local treatment.		Source of Funding: None declared Comments: All patients use emollients daily. 'Some' used topical treatments (TCS and/or tacrolimus).

Bibliographic details	Study type and evidence level	No. of patients	Patient characteristics	Intervention & comparison	Outcome measures, follow-up and effect size	Comments
Tzung TY;Lin CB;Chen YH;Yang CY; 2006 431	Study Type: Randomised Controlled Trial Evidence Level: 1-	Total number of patients = 26 Pimecrolimus cream 1% applied to all skin lesions twice daily + narrowband UVB to one half of body twice weekly N = 12 Pimecrolimus cream 1% applied to half the body twice daily + narrowband UVB irradiation to whole body twice weekly N = 14	Children and adolescents aged 5-17 years with moderate to severe atopic eczema. IGA mean score 4.2, mean EASI score 30.5 (12.2-52.5), and mean body surface area affected 48.5 (range 15-95). Mean pruritus score 6.9 (on 10cm VAS). Exclusions: those receiving treatment with antihistamines, systemic corticosteroids, immunosuppressive therapy, Chinese herbal medicine or phototherapy within 3 months; TCS or antihistamines within 1 week.	Pimecrolimus whole body + narrowband UVB to half body (within-patient comparison) vs Pimecrolimus half body + narrowband UVB to whole body (within-patient comparison)	Outcomes at 6 Weeks: EASI (mean score change) -53% pimecrolimus-only body half -56% pimecrolimus +narrowband UVB body half (p=0.002 for both sides vs baseline, and p=0.084 between halves) -55% pimecrolimus-only body half -59% pimecrolimus +narrowband UVB body half (p=0.002 for both sides vs baseline, and p=0.059 between halves) Pruritus (mean score change) overall mean score reductions of 3.0 or 3.1 (p<=0.004) - unclear which group which result relates to Adverse effects none vs 14% (n=2) intractable generalised pruritus and tender erythema	Source of Funding: None declared Investigators were blind to treatment allocation - unsure how blinding can be maintained when irradiation leads to erythema. UVB irradiation was performed using 24 Waldmann fluorescent tubes mounted in a UV 5001BL cabinet. The starting dose was 70% of the predetermined minimal erythema dose for each patient, with increments every week to a maximum of 1.5J/square cm. When UVB irradiation was given to half the body, the other half was shielded using UV-filtering clothing. The EASI scores were reported as within-patient left-right side comparisons. No other active treatments (including emollients) were allowed during the study.

Bibliographic details	Study type and evidence level	Study aims/objectives	No. of patients	Patient characteristics	Outcomes	Comments
Silva SH; 2006 [432]	Study Type: Cohort Study Evidence Level: 2-	To consider the effects of UVB phototherapy on microorganisms on skin.	Total No. of Patients = 20 Children with AE treated with narrowband UVB phototherapy N = 10 Children with vitiligo treated with narrowband UVB phototherapy N = 10	Children mean age 114 months (9.5 years) with moderate severe atopic eczema (mean SCORAD score 71, median 73, range 62-82). The children in the control group had vitiligo and were of the same mean age.	SCORAD (mean score change, AE only) -22.4 (31%), p<0.05 vs baseline Total cutaneous aerobes (log CFU/square cm)* -0.27 vs -0.21 Total cutaneous anaerobes (log CFU/square cm)* -0.20 vs -0.13 Total cutaneous Staphylococci (log CFU/square cm)* -1.02 vs -0.15	Funding: Grants from Brazilian ministries *change from before to after UVB. UVB exposure was similar in children with AE and vitiligo (accumulated joules 4.3 SD 0.9 vs 4.3 SD 0.8 respectively). Duration of exposure and of follow-up was not stated. All changes in levels of cutaneous microbes were reported to be statistically significant (p<0.05), but it is not clear whether this is from baseline or between groups (or both). Isolation frequency and toxins of S.aureus were also reported - data not reproduced here.

Bibliographic details	Study type and evidence level	No. of patients	Patient characteristics	Intervention & comparison	Outcome measures, follow-up and effect size	Comments
Atherton DJ; 1988 Jun 439	Study Type: Case series Evidence Level: 3	To describe the use of psoralen photochemotherapy (PUVA) in adolescents	Total No. of Patients = 15 PUVA (8-methoxypsoralen 0.6mg/kg + UVA irradiation) N = 15	Children aged 10-14.7 (median 13.6) years with severe atopic eczema which had proved refractory to other forms of treatment. Most (unknown number) became unable to attend school because of the severity of their eczema. Ten children also had asthma, whose height was on or below the third centile at the start of treatment.	Clearance/near-clearance 14 (93%) (1 withdrew as unable to tolerate the heat of the UVA cabinet) Time to remission 0.3-1.8 years (median 1 year) Duration of remission 0-25-4.2 years (median 1.1 years) Adverse effects 20% freckles 7% (n=1) cutaneous herpes simplex 1 photo-onycholysis	Source of Funding: None declared Comments: 8-methoxypsoralen was given 2 hours before irradiation. The duration of treated is unknown. Nine children received irradiation three times a week, and six twice a week. The initial dose was 1 J/square cm, gradually increasing by increments of 0.5-2.0 J/square cm until clearance or near-clearance (not defined) achieved. Maintenance treatment was used after clearance, with the freqeuncy gradually reduced. Short courses of oral prednisolone were used in 5 (33%) when it was not possible to increase the UVA exposure adequately due to skin irritability. At clearance the dose of UVA given was 2-15 (median 9) J/square cm; cumulative dose 50-590 (median 155).
Sheehan MP; 1993 Oct 438	Study Type: Case series Evidence Level: 3	To document the experience of using PUVA in children.	Total No. of Patients = 53 Photochemotherapy (8-methoxypsoralen 0.6mg/kg 2 hours before UVA exposure) twice or three times a week N = 53	Children aged 6-16 years (mean 11.2 years) with severe atopic eczema that: 1) 'substantially disabled' them educationally, physically, socially, and/or emotionally 2) had failed to respond to intensive topical treatment with emollients and TCS.	Response 74% at least 90% clearance (after mean 9, median 11 weeks treatment, range 6-28)* 26% did not achieve clearance or near-clearance (21% discontinued treatment)* Relapse 69% in remission (none requires dialy skin treatment) Adverse effects	Source of Funding: None declared Comments: UVA was administered using a standard stand-up 7001k UVA Waldmann machine. A standard 1 J/square cm was used as the initial dosage, which was gradually increased to 0.5-2.0 at intervals no less than 1 week. After clearance a period of

Bibliographic details	Study type and evidence level	No. of patients	Patient characteristics	Intervention & comparison	Outcome measures, follow-up and effect size	Comments
				The children were also required to have normal renal and hepatic function.	30% development of freckles 19% blistering 9.4% recurrent herpes simplex 3.8% acute exacerbations of asthma No evidence of corneal or lens opacities Liver function tests remained normal	stabilisation was allowed during which UVA was continued at the same frequency for a number of weeks (never less than 2 weeks, nor greater than 12 weeks - 4-6 weeks was usual). *at the time of clearance the UVA dose ranged from 2-15J/square cm (mean 8), the cumulative dose 180-470 (mean 280), and number of treatments 12-84 (mean 19, median 27). In those who discontinued the cumulative dose was 320-2020 (mean 980), and number of treatments 24-67 (mean 45, median 48). In 32% the psoralen dose was changed to 5-methoxypsoralen as was permitted in the protocol for excessive erythema and/or pruritus (dose 1.2 mg/kg). Following reduction in treatment frequency, 82% of those whose AE cleared subsequently discontinued treatment (duration of treatment 13-116 weeks, mean 31). The cumulative UVA dose was 97-3870 J/square cm (mean 1118, median 1308), total number of treatments 31-176, mean 59, median 65). 38% also received oral prednisolone during the early phase of treatment to allow increases of UVA exposure, the prednisolone was then gradually tapered off. The cumulative dose of those also treated with prednisolone was less than the total group (mean 870, median 922 J/square cm) as was the

Bibliographic details	Study type and evidence level	No. of patients	Patient characteristics	Intervention & comparison	Outcome measures, follow-up and effect size	Comments
						number of treatments (mean 52, median 59).
Collins P; 1995 Oct 436	Study Type: Case series Evidence Level: 3	To document the authors experience of using narrowband UVB, and to discuss its potential (letter).	Total No. of Patients = 40 Narrowband UVB phototherapy N = 40	Children aged 2.5-15 years (median 11 years) with atopic eczema, severe in 50%, moderate in 48%, and mild in 2%. None had previously had phototherapy or photochemotherapy.	Response 23% excellent (not defined) 58% good 20% poor (treatment discontinued) Relapse Data for 24 of the 32 who completed treatment: 20% relapsed within 6 weeks 50% relapsed at 3-4 months 25% relapsed at 6-9 months 5% remained clear 2 years later Adverse effects 50% truncal erythema 35% facial erythema 25% xerosis 5% herpes labialis 2.5% burning	Source of Funding: None declared Comments: The minimal erythema dose ranged from 70-770 mJ/square cm (median 240, mean 301). Cumulative dose range 2225-49,067 (median 16,371, mean 17,887). Total number of exposures 12-58 (median 24, mean 26). The data were reported within a letter. Use of emollients was encouraged during the study, and weaning off TCS depending on their condition.
Tay Y; 1996 433	Study Type: Case series Evidence Level: 3	To report the authors experience of using UVB phototherapy in children with skin conditions.	Total No. of Patients = 20 Phototherapy (UVB) N = 5	Children aged 14 months to 12 years with various skin conditions treated with phototherapy (25% had atopic eczema). Those with atopic eczema were aged 16 months to 11 years (mean 7 years), had the condition for 1-9 years (mean 3.4 years). All had disease covering at least 50% of the body surface area, and was not controlled with TCS, emollients and antibiotics.	Response No numerical data. It was reported that 'none healed completely but all were moderately improved, with a reduction in extent of eczema and in pruritus'. TCS use was 'less' - no numerical data. Adverse effects 40% (n=2) erythema and burning after some of the treatments, necessitating temporary discontinuation of treatment	Source of Funding: None declared Comments: The number of treatments ranged from 20-61 (mean 41) over 7-20 weeks (mean 15). Cumulative dose range 2.39-7.78 J/square cm (mean 5.6).
Pasic A; 2003	Study Type: Case series	To report the authors' experience with phototherapy in children with UV-responsive skin	Total No. of Patients = 57 Combination of UVA and UVB irradiation three or five	Children aged 4-16 years with various skin conditions, including	Response 45% 'almost complete disappearance of eczema and pruritus'	Source of Funding: None declared

Bibliographic details	Study type and evidence level	No. of patients	Patient characteristics	Intervention & comparison	Outcome measures, follow-up and effect size	Comments
[434]	Evidence Level: 3	disorders.	times a week N = 21	atopic eczema in 37%. In those wtih AE the age range was 4-15 years, mean 11.5 years. The condition covered at least 40% of their body surface area despite the use of emollients, TCS, antihistamines, antibiotics. Ten had a positive family history of atopic, sic had coexisting hayfever.	23% good response 32% moderate response Adverse effects 19% mild erythema	Comments: The whole body was irradiated including the face. Excellent response = greater than 90% reduction in SCORAD score, good 70-90% reduction, moderate 50-70% reduction. Cumulative UVB dose 1.3-10.42 J/square cm (mean 6.14). Mean 18 treatment received, range 9-71. Cumulative UVA dose 27.5-182 J/square cm (mean 69.7). Mean 18 treatment received, range 9-47. Duration of treatment unclear.
Jury CS; 2006 Mar [435]	Study Type: Case series Evidence Level: 3	To describe experience of using narrowband UVB in patients aged 16 years and under.	Total No. of Patients = 77 Narrowband UVB phototherapy N = 25	Children treated with narrowband UVB phototherapy for various skin conditions (32% atopic eczema). Age range of the total group 4-16 years, median 12 years. Demographic detail not reported separately for the atopic eczema subgroup.	Response (in AE group) 68% achieved minimal residual disease at treatment end 16% 'no better' No outcomes documented for the remaining 16% of patients. Adverse effects (total group) 30% erythema 6.5% anxiety 2.6% Herpes simplex infection (both AE patients) - did not progress to eczema herpeticum 1.3% (n=1) varicella zoster infection	Source of Funding: None declared Comments: Response was recorded as clear, minimal residual disease, no better, worse, or failed to attend follow-up. Phototherapy: a minimal erythema dose was established in 42%, who received a starting dose of 50% of the minimal erythema dose. The starting dose in the remainder was empirical. 20% increments were used in most cases, reducing to 10% increments where necessary. Overall in the 77 patients, 103 treatment courses were administered, with 18 children receiving more than one course.

Bibliographic details	Study type and evidence level	No. of patients	Patient characteristics	Intervention & comparison	Outcome measures, follow-up and effect size	Comments
						In children with atopic eczema who received more than one course (number unknown), the mean number administered was 2.1 (range 2-3). The frequency of phototherapy within a treatment course was not stated, nor was the duration of a treatment course.
Clayton TH; 2007 [437]	Study Type: Case series Evidence Level: 3	To assess improvement of AD in children who had undergone NB-UVB phototherapy	Total No. of Patients = 60	Age range 4-16 years (median 12 years), AE patients who had undergone narrow-band UVB phototherapy between 1999 and 2005 in a single hospital	Adverse events recorded in 14 patients: well-demarcated erythema, painful erythema and reactivation of herpes simplex. No improvement was reported in 7 children.	

Complementary therapies

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Witt CM; Lüdtke R; Baur R; Willich SN; 2005[469]	Study type: Prospective multicentre observational cohort Evidence level: 3	3,981 adults & children 1,130 were children of which 20% had a diagnosis of atopic eczema (n=226)	Chronic conditions (97% of diagnoses) including children with atopic eczema Mean age (± SD) of all children 6.7±4.1years Primary care Germany	To investigate on a range of diagnoses (including atopic eczema), course of treatment, and long-term outcome in those who chose to receive homeopathic medical treatment by standardised questionnaire	Follow up period: 24 months Intervention: Children's and physician's assessments (0-10) and quality of life at 0,3,12,24 months (KINDL) Quality of life assessed by parent for children under the age of 6 years (KITA) Comparison: Children acted as their own controls, differences from baseline to end of study. Safety: No measures	No effect size calculated Atopic eczema data not presented separately Disease severity decreased between 0-24 months by both child 6.1±1.8- to 2.2±2.0 (SD) & physician assessment 5.9±1.7 to 1.5±1.8 both p<0.001 versus baseline. Improvement in quality of life of all young children (data not presented separately)	Findings indicate that homeopathic medical therapy may play a beneficial role in the long-term care of patients with chronic diseases.	Methodological quality poor (uncontrolled, no details of treatments, data not presented by diagnosis group, quality of life data assessed by parent if child under 6 years but data not given separately) No safety data given
Mohan GR; Anandhi KS; 2003[470]	Study type: Uncontrolled case series Evidence level: 3	n=36	Various age groups including 9 children (11 months-12 years) with mild to moderate symptoms except one with severe symptoms. 2 groups: skin symptoms only (n=6) and skin & respiratory symptoms (n=3) in an Indian	Intervention Individualised homeopathic treatment for 5 years Comparison None Concomitant treatment	Follow up period: 5 years Outcome measure Effectiveness On observation of no less than 6 months positive result: a) relief (76-99%) of the	Skin symptom only group: 3/6 were rated 99% with no new exacerbation 2/6 were rated 60% with occasional exacerbation 1/6 was rated 20% and discontinued treatment	Findings indicate that homeopathic medical therapy may play a beneficial role in the long-term care of patients with atopic eczema without undue side effects.	Methodological quality poor (uncontrolled and small numbers Lack of detail of clinical symptoms

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
			homeopathic medical college	Regular counselling on diet, maintaining dust and stress free environment. Liquid paraffin for dry skin	symptoms with no new exacerbation b) relief (51-75%) of the symptoms with occasional exacerbation c) relief(26-50%) of the symptoms with new recurrence Negative result 0-25% relief of symptoms, no change in skin condition or with new recurrence Safety No measures			
Sheehan MP; Atherton DJ; 1992 [471]	Study type: RCT Placebo controlled, double blind crossover study Evidence level: 1-	n= 47 enrolled 37 completed the trial No numbers for each arm of study	37 children with non exudative atopic eczema Age range 1.5-18.1 years. Mean age: 9.1 years Tertiary referral centre	Intervention: Chinese herbal combination product Provisional identification of components: *Ledebouriella sesloides, Potentillia chinensis, Anebia clematidis, Rehmannia glutinosa, Paeonia lactifora, Lophatherum gracile, Dictamnus dasycarpus, Triculus terrestris, Glycyrrhiza uralensis and Schizonepeta tenuifolia*	Follow up period: 20 weeks Outcome measures: Effectiveness Mean severity score (0-3) and percentage coverage of erythema and surface damage Parents were asked to state a preference based on their children's sleep Safety Questionnaire seeking evidence for possible adverse events	Effectiveness Median percentage decrease in erythema scores during active phase 51.0% (95% CI 34.5% to 72.6%) compared to 6.1% (-25.2% to 30.7%) during the placebo phase. (95% CI for the difference 13.4% to 89.7%) Median percentage decrease in surface damage scores during active phase 63.1% (95% CI 34.5% to 72.6%) compared to 6.2% (-25.2% to 30.7%) during the placebo phase. (95% CI for the difference 19.2% to 97.9%)	Chinese medicinal herbs provide a therapeutic option for children with extensive atopic eczema that has failed to respond to other treatments. In the medium term, it proved helpful for approximately half the children who originally took part in the trial. The possibility that it may provoke hepatic abnormalities requires further study.	Small study with some compliance and long time safety issues. This product (Zemaphyte) is no longer being manufactured

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				Comparison: Placebo consisting of a mixture of inert plant matter: *Humulus lupulus*, *Hordeum distichon*, *Hordeum distichon ustum*, *Bakers bran*, *sucrose*, *Salvia spp. Thymus vulgaris*, *Rosmarinus offincinalis*, *Mentha piperita*, *clove oil* and *Glycyrrhiza uralensis.* Children were supplied with two types of sachets, parents prepared decoctions according to the child's age: age 1-7 years two large and two small sachets daily; age 8-13 years: three large and three small sachets; age >14 years: four large and four small sachets daily. Decoction taken orally as 100ml liquid whilst still warm. All children received both	A 24 hour urine sample was taken at start and end of each treatment (n=3) for measurement of creatinine and endogenous corticosteroid excretion	Improved sleep was reported in 19 cases during active phase, 3 in placebo phase and no change was noted for the remaining 15 cases Parent's preference 27 cases reported superiority of the active phase, 2 cases for placebo, 8 cases had no preference Safety There was no evidence of haematological, renal or hepatic toxicity.		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				treatments for 8 weeks with a 4-week wash out period in between.				
Sheenan MP; Atherton DJ; 1994[472]	Study type: One year uncontrolled follow up of Sheenan MP; Atherton DJ; 1992[7] Evidence level 3	n=37 14 children withdrew within that year	Children who had completed an RCT of Chinese medicinal herbs for atopic eczema Of the 23 children completing age range was 1.5-18.1 years, mean age 9.1 years	Intervention: Chinese herbal mixture Provisional identification of components: *Ledebouriella sesloides, Potentillia chinensis, Anebia clematidis, Rehmannia glutinosa, Paeonia lactifora, Lophatherum gracile, Dictamnus dasycarpus, Triculus terrestris, Glycyrrhiza uralensis and Schizonepeta tenuifolia* Children were supplied with two types of sachets, parents prepared decoctions according to the child's age: age 1-7 years two large and two small sachets daily; age 8-13 years: three large and three small sachets; age >14 years: four large and four small	Follow up period 1 year Outcome measures Effectiveness 3 month assessments Mean severity score (0-3) and percentage coverage for erythema and surface damage. Blood pressure measurements & total serum IgE Safety 6 month assessments full blood count, serum sodium, pottasium, urea, creatinine,calcium, phosphate, bilirubin, AST and alkaline phosphatase	Effectiveness 7/23 were able to discontinue treatment after achieving at least 90% reductions in eczema activity scores and this was maintained until the end of the study 16/23 continued treatment for the year to maintain improvement. At the end of study 11/16 had a 90% reduction of eczema scores, 1/16 reduction between 60% and 89%, 4/16 had reduction between 30-59%. Blood pressure was normal throughout study. 21/23 children had elevated IgE levels prior to the original study 10/23 showed a >10% decrease over the year. 3/23 showed a >10% increase over the year. Safety Serum AST levels exceeding 1.5 times the upper limit of normal was recorded on a single occasion in two children. In both children treatments were stopped. Serum AST for all other children and all other biochemical	Chinese medical herbs provide a therapeutic option for children with extensive atopic eczema that has failed to respond to other treatments. The possibility that it may provoke hepatic abnormalities requires further studies.	A mild laxative effect was noted by approximately one third of patients during the first few weeks but this caused no compliance problems This product (Zemaphyte) is no longer being manufactured.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				sachets daily. Decoction taken orally as 100ml liquid whilst still warm. Comparison: All children/parents opted to have the active treatment Children were seen at 3 month intervals Daily treatment was continued until reduction of 90% was recorded in both erythema and surface damage scores. Treatment frequency was then gradually reduced at 6 week intervals, provided that the level of benefit was maintained		parameters within normal range throughout the study.		
Hon KLE; Leung T; Wong Y; Lam WC; Guan DB; Ma KC; Sung YR; Fok T; Leung P; 2004[474]	Study type: Uncontrolled case series Evidence level: 3	9 children All completed, one showed 75% adherence	Chinese children with atopic eczema with a SCORAD index of ≥15 Median age 11.3 (5-13.5) years in a paediatric dermatology outpatient clinic	Intervention 3 pentaherb capsules twice daily for 4 months Formulation: Flos Lonicerae (Jinyinhua)2g, Herba Methae	Follow up period: 4 months Outcome measures Effectiveness SCORAD index monthly	The overall SCORAD score before and at the end of 3 months was 60.3 (20.0-82.6) and 40.0 (11.4-56.5) respectively (p=0.008) The extent, intensity, prutius and sleep loss components of SCORAD were also significantly improved (p<0.05 for all)	Pentaherb capsules were well tolerated by children and apparent beneficial effects were noted clinically.	Methodological quality poor (uncontrolled,& small numbers)

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				(Bohe) 1g, Cortex Moutan (Danpi) 2g, Rhizoma Atractylodis (Cangzhu) 2g and Cotex Phellodendrie (Huangbai) 2g which makes 6-7 capsules Comparison None	Safety biochemical tests	No clinical or biochemical evidence of adverse events		
Schacher L; Field T; Hernadez-Reif; Duarte AM; Krasnegor J; 1998[487]	Study type: RCT Unblinded study Evidence level: 1-	n=20 children 10 children in each group	Children with atopic eczema Age range 2-8 years Mean 3.8 years	Intervention: All children continued to receive usual care (emollients and topical corticosteroids) Intervention 20 minute daily massage with emollient by parents (initial session taught by therapist) Comparison: Usual care alone	Follow up period: 1 month Outcome measures: Effectiveness *Pre and post therapy sessions*: Parent measure of STAI (20 items) Child measures using Happy Face Scale (1-4) Researcher measure Behavioural Observation Scale: affect, activity, anxiety *First and last day assessments*: Parent measure of Tactile Defensiveness Scale, Coping index (0-4), How I feel about my child (17 item) , Likert scale (5 points) Skin assessment focal & global Scale of 0-3 on redness, lichenification,	*Pre and post therapy sessions* STAI statistically significant improvement in massage group between first and last day (41.5, 35.3 p=0.05) Control group no differences Happy faces: no differences in both groups Behavioural observations: massage group improved statistically significant only on last day: p=0.05 for all. Control group no differences *First and last day assessments* Tactile defensiveness scale : no statistical differences in either group Coping index: massage group improved in 3/6 measures on last day, anxiety (p=0.05), stability (p=0.05), feeling about child (p=0.01). Control group no differences	These data suggest that massage therapy may be a cost effective adjunct treatment for atopic eczema, since there is a one time expense of $30 for the child to receive the massage and the parent to learn the technique	Encouraging data but small sample size relatively short duration of intervention, lack of blinding for children and parents Comparisons are with baseline within each treatment group, rather than between treatment groups. Need for further research. No safety data reported

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
					scaling, excoriation and pruritus. Safety No measures	Skin assessments on last day: Massage group improved in focal area redness (p=0.001), lichenification (p=0.05), scaling (p=0.05)), pruritus (p=0.05), excoriation (p=0.1) & global area scaling and excoriation (p=0.05) Control group No differences except in focal & global area scaling (p=0.05)		
Sokel B; Christie D; Kent A; Lansdown R; Atherton D; 1993[484]	Study type: RCT unblinded study Evidence level: 1-	n= 45 enrolled complete data for 31 children Biofeedback group (n=9) Hypnotherapy : (n=12) Discussion group (n=10) All children were stabilised on topical and oral treatment in a 2 week run in period	Children (5-15 years) with atopic eczema (5-14.7 years) Mean age: 8.9 years	Intervention: Biofeedback group (relaxation which did not include imagery) Hypnotherapy group (relaxation that focused specifically on reducing itching) Comparison: Discussion group (attention placebo) All children received four 30 minute sessions with a psychologist 2,3,5 and 8 weeks after enrolment	Follow up period: 20 weeks Outcome measures: Effectiveness Mean severity score (0-3) and percentage coverage for erythema, surface damage and lichenification at 0, 8 and 20 weeks, determined by a dermatologist blinded to treatments Safety No measures	Effectiveness There were no significant differences in severity of erythema across groups or time. With severity of surface damage there was a significant interaction between intervention groups (pooled) vs. discussion and time p=0.046) Severity of lichenification was significantly improved between intervention groups (pooled) and discussion group at visit 3 (20 weeks) (p=0.02) There was no significant difference in the percentage of body area covered for erythema, lichenification or surface damage at any time point.	20 weeks after entry to the trial the children in the two relaxation groups showed a significant reduction in the severity of surface damage and lichenification compared with the control group.	Methodologically poor, small study, lack of blinding, relatively short Possible post-hoc analysis of final data. No safety data reported
Derrick EK; Karle H;	Study type:	n=11	Children with	Intervention	Follow up period :	Median improvement in	Some benefit from the self	Methodologically poor:

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Darley:CR; 1994[485]	Uncontrolled case series Evidence level 3		established atopic eczema severe enough to require regular TCS (age range 5-12 years) Uk dermatology unit	After initial control period, taught self-hypnosis by a guided imagery technique Comparison None Children were treated in a standard way with emollients and TCS throughout study	18 weeks Outcome measures: Effectiveness eczema score of a maximum of 18: dryness, lichenification, crusting, erythema, excoriations and extent scored 0-3 at 6 visits patient diary Safety No measures	total eczema score between visit 1 and 6 was 2.6 (p=0.139) and between visit 3 and 6 (period of self hypnosis) 1.75 (p=0.169) Only 2 patients maintained home diaries	hypnosis technique on the children's eczema was observed although this did not reach statistical significance	uncontrolled and small numbers
Stewart AC; Thomas SE; 1995[486]	Study type: Uncontrolled case series Evidence level 3	n=20 children and 1 adult	Children with severe refractory atopic eczema (age range 2-15 years) UK dermatology unit	Intervention Individualised tape of Magic Music incorporating elements of relaxation, stress management ego strengthening, skin comfort and post hypnotic suggestions to use nightly Comparison None	Follow-up period: 18 months Outcome measures: Effectiveness Assessments of eczema were made at 3 consecutive clinic appointments using the scale of mild, moderate or considerable Questionnaire at 18 months asked about any change in itching, scratching, sleep disturbance and mood. Unaltered, improved or worsened (a little or a lot) Safety	Pictorial data only were shown on severity of eczema. Marked improvement was reported. Of the 12 responses to the questionnaire, 10 children had maintained improvement in itching, scratching, sleep disturbance and 7 with regard to improvements in mood.	These preliminary results indicate that a larger study with controls and more detailed pre-treatment assessment of the children's eczema would be useful in evaluating the benefit of hypnotherapy in atopic eczema	Methodologically poor: uncontrolled and small numbers

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
					No measures			
Anderson C; Lis Balchin M, Kirk-Smith M; 2000 [488]	Study type: RCT Unblinded study Evidence level:-1-	n=16 n=8 for aromatherapy massage n=8 massage alone	16 children with atopic eczema born to middle class mothers Age range 3-7 years Mean age not reported	Intervention: Massage with essential oils plus counselling from a therapist weekly plus daily treatment from mother. Choice of 36 oils of which the most popular were sweet marjoram, frankincense, German chamomile, myrrh, thyme, benzoin, spike lavender and *Libea cubeda* diluted in almond carrier oil. Comparison: Same treatment with almond carrier oil only	Follow up period 8 weeks Outcome measures: Effectiveness Daily day time irritation scores & night time disturbance scores (both 0-10) before and after treatment assessed by mother General improvement scores (0-10) after 2 weeks by GP, therapist, and mother Differences from baseline to end of study (child acting as on control) Plus inter group differences. Safety No measures	Effectiveness Significant improvement of eczema but no differences between groups in both groups. Pre-during data Daytime irritation score Aroma: 4.7 ±1.6, 2.13 ± 0.45 p=<0.02 Massage: 5.70±2.39, 4.70±2.88 p=0.002 Nighttime irritation score Aroma: 2.33±0.72,0.94±0.1 p=0.002 Massage: 2.06±0.52,1.14±0.26 P=0.002 General improvement score by GP, therapist, and mother Aroma 2.8±0.65, 3.9±0.67, 5.4±0.62 Massage 3.0±0.6, 4.0±0.91, 6.3±0.59 Safety No safety issues experienced during trial but further treatments with essential oil massage showed deterioration in the eczematous condition after two further 8-week periods of therapy. This may have	A significant improvement in the eczema in the two groups of children following therapy, but there was no significant difference in improvement shown between the aromatherapy massage and massage only group. Thus there is evidence that tactile contact between mother and child benefits the symptoms of atopic eczema but that adding essential oils is no more beneficial than massage alone.	Small, unblinded trial, with various interventions i.e. choice of essential oils used Plus potential long-term adverse events

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						been due to a decline in the novelty of the treatment, or, it strongly suggests possible allergic contact dermatitis by the essential oils.		
Al-Waili NS: 2003 [489]	Study Type: Controlled single-blind study Evidence level 2-	n=21 Group 1: n=10 who were having no treatment at start of study Group 2: n=11 who were undercurrent treatment with TCS United Arab Emirates dermatology unit	21 children with moderate to severe eczema (Aged 5-16 years)	Intervention Group 1: Lesions on right side of body treated with Vaseline, left side with honey, beewax and olive oil mixture (1:1:1) three times daily for 2 weeks If no response recorded as failure. If response to honey mixture, Vaseline was replaced by honey mixture for up to 6 weeks Group 2: Lesions on right side of body treated with Vaseline and 0.1% betamethasone esters (v/v1:1), left side with mixture A for 2 weeks If response to Vaseline, treatment was continued and patients were removed from	Follow up period: 6 weeks Outcome measures: Effectiveness Body lesions assessed by study author for erythema, scaling, lichenification, excoriation, induration/papulation, oozing/crusting and for the reported intensity of pruritis. Severity on a 0-4 scale (none, mild, moderate, severe very severe) at each visit Safety No measures	Main assessment was at 2 weeks Group1: 8/10 children showed improvement with honey mixture Mean score 6.7±5.3. Significantly improved from baseline line and Vaseline treatment ($p<0.05$). All children treated with honey mix for next 4 weeks and continued 0i improve significantly from baseline ($p<0.0001$) Group2: 5/11 patients showed no deterioration upon 75% reduction of TCS with the use of mixture C. Mean scores at 0 & 6 weeks were comparable	The honey mixture may be useful adjunct in the management of atopic eczema although there is no clear rationale behind treatments.	Complex and low quality study

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				study. If no response to Vaseline mix,, treatment was replaced with mixture A. If response to mixture A, Mixture B was used for next 2 weeks, if response again, mixture C was used for last 2 weeks (total 6 weeks) Mixture A: honey mixture with TCS ointment (v/v 1:1) Mixture B: honey with TCS (v/v2:1) Mixture C: honey mix with TCS (v/v 3:1) Type of TCS as patients prescription prior to study				
Kalus U; Pruss A; Bystron J; Jurecka M; Smekalova A; Lichius J; Kieswetter H; 2003 [490]	Study type: Clinical paper reporting 4 studies of which 2 were relevant a) 1RCT evidence level 1- b) Uncontrolled study evidence level 2-	a) RCT n=63 atopic patients of which n=9 had atopic eczema n=6 treatment n=3 placebo b) uncontrolled study n=49 of atopic patients of which n=6 with atopic eczema	a) 9 children with atopic eczema, (no detail on status of eczema) (Aged 6-17 years) b) 6 children with atopic eczema, no detail on status of eczema) (Aged 6-17 years	Intervention One black seed (*Nigella sativa*) oil capsule three times daily for 8 weeks Comparison One placebo oil capsule three times daily for 8 weeks Treatment was	Follow up: 8 weeks Outcome measures Effectiveness Subjective feeling of improvement Biochemical tests	Clinical improvement occurred in 2/6 patients the drug compared to 1/3 patients in the placebo group No other clinical data IgE levels and eosinophils count were unchanged One child of the 63 reported gastrointestional problems	Black seed oil may be beneficial adjuvant treatment to the treatment of atopic eczema but the numbers of children tested and paucity of outcome data make it impossible to be definitive Black seed oil may be beneficial adjuvant treatment to the treatment of atopic eczema but the numbers of children tested and paucity of outcome data	Despite being a RCT, numbers were low and clinical outcomes inadequate Uncontrolled study and adverse events

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				started at first sign of symptoms No details of other treatments Intervention 2 capsules of black seed oil three times daily for 6-8 weeks Comparison None	Safety Self reporting Follow up: 6-8 weeks Outcome measure: Effectiveness Subjective feeling of improvement Safety Self reporting	3/6 children improved, 2/6 remained unchanged, 1/6 had deterioration No other clinical data Gastrointestinal complaints occurred in 9/49 children taking capsules on an empty stomach. The dose of 80mg/kg body weight too high	make it impossible to be definitive	
Berth-Jones; Graham-Brown; 1993 [65]	Study Type: RCT Double-blind, placebo controlled, parallel group study Evidence level:1+	n=133 Two age groups 7-12 years & 13-60 years Under 12 years Placebo n=20 EPO n=21 Fish oil n=21 n=27 of adults & children had defaulted or been withdrawn by end of study	62 children with atopic eczema Co-treatments included weak topical steroids, emollients	Intervention: 6 capsules each containing 500mg of EPO Or 6 capsules each containing 107mg of fish oil Comparison: 6 capsules of placebo (olive) oil Administered twice daily. Capsules were cut open if necessary to administer to children	Follow up period 16 weeks Outcome measures: Effectiveness SASSAD score: Body divided into 10 zones, each scored 0 (absent) to 3 (severe) for erythema, excoriation, dryness, cracking and lichenification Percentage of skin affected Topical steroid requirement Patient diaries with visual analogue scales for itch, dryness, scaling, redness and overall impression for 24 weeks	No separate analysis for adult and children's data. Authors state separate analysis gave results similar to the overall analysis. Effectiveness: At 16 weeks, there was no statistically significant improvement in the Leicester scores with either active treatment different from placebo (p=0.74, p=0.26 respectively) Mean changes in individual components of the SASSAD score showed no differences between active treatments and placebo except for in favour of placebo over fish oil in erythema (p=0.04) and cracking (p=0.05). Mean percentage of skin surface affected fell by 3.26% (4.49%; 33) with EPO and 0.11% (4.56%; 35) on fish oil and rose by 3.62%(3.52%; 34) with	The study found no effect of essential fatty acid supplementation in atopic eczema.	Good quality RCT No individual reporting of children's data

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
					Safety No measures	placebo. There were no statistically significant differences. There was a reduction in steroid requirement in all three groups with the largest reduction in the placebo group. The greatest mean overall reduction in visual analogue scales was seen in the placebo group No significant differences in response to treatment between 'allergic' and 'non-allergic' children thus data were pooled.		
Biagi PL; Bordoni A; Hrelia S; Celadon M; Ricci GP; Cannella V, Patrizi A; Specchia F; Masi M; 1994 [492]	Study Type: RCT Double blind, placebo-controlled study Evidence level: 1+	n= 51 mean age 4.2 years Range 2.2 to 8.5 years Children were divided into 2 groups: a) non-allergic (normal Ig E, negative RAST & PRIST test) N=25 b) allergic (raised >100iU/ml IgE, Positive RAT & PRIST test) n=23 3 children failed to attend follow up. Children in Group a) & b) were randomised to one of the three groups n=16 in	Children with a diagnosis of atopic eczema according to the method of Hanjfin & Rajka Co-treatments included weak steroids, emollients	Intervention: High dose evening EPO (0.5g/kg/day) Or Low dose EPO 50% mix 0.5g/kg/day + placebo capsules Comparison: Placebo olive oil=10mg Vitamin E	Follow up period: 8 weeks Outcome measures: Effectiveness: Rating scale (0-3) where 0= absent, 3=severe on 10 clinical features: erythema, scaling, crusting, oedema, vesiculation, evidence of infection, lichenification, pigmentation, papules & excoriation. Pruritus was assessed separately on a 0-3 scale All children were assessed for their allergic status using IgE, RAST, PRIST tests Safety: No measures	Effectiveness: Clinical assessment scores at baseline and end of treatment showed there was a trend towards improvement in the low dose group which approached significance (p=0.077) and a significant improvement in the high dose group compared with placebo (p=0.046). For prutitus there was a trend towards improvement in both EPO compared with placebo but it did not reach statistical significance.	The overall severity of atopic eczema improved significantly on a high dose of evening primrose oil compared with placebo, independent of whether the children had manifestations of IgE-mediated allergy.	Good quality trial but clinical features were analysed as a whole. Individual analysis would have been of more use.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
		each						
Bordoni A; Biagi PI; Masi M; Ricci G; Fanelli C; Patrizi A; Ceccolini E; 1987 [491]	Study type; RCT Double blind placebo controlled study. Evidence level: 1+	n=24 Children aged 2-4 years. EPO n=12 Placebo n=12	Children with a diagnosis of atopic eczema according to doctor Co-treatments included mild topical steroids, emollients, oral antihistamines.	Intervention: EPO, six 0.5g capsules daily Comparison: Six capsules of olive oil (placebo).	Follow up =4 weeks Outcome measures: Effectiveness Clinical evaluation by rating scale for erythema, oedema, vesiculation, crusting, excoriation, scaling, lichenification, pigmentation, pruritus, loss of sleep on a 0-3 scale with 0= absent 3= severe from which a total eczema score. 4 groups of clinical change: improved <10 points or more Moderately improved <5-10 points Unchanged < or > of 4 points Worse increase of >5 points Safety No measures	Effectiveness: After 4 weeks symptoms of children treated with EPO significantly improved (P<0.01). Placebo-treated children clinical status remained largely unchanged EPO group 4 children improved, 4 moderately improved, 3 unchanged, 1 worse. Placebo group 0 children improved, 1 moderately improved, 10 unchanged, 1 worse.	Evening primrose oil substantially improved the clinical symptoms of atopic eczema in two thirds of the treated children after 4 weeks.	Small study but clinical features were analysed as a whole. Individual analysis would have been of more use. Improvement was from baseline.
Takwale A; Tan E; Agarwal S; Barclay G; Ahmed I; Hotchkiss K; Thompson JR; Chapman T; Berth-Jones J; 2003 [493]	Study type; RCT Double blind placebo controlled study. Evidence level: 1+	n=140 including 69 children n= 40 borage oil n=29 placebo Number of children completing trial was not reported but 16 participants	Children over the age of 2 years with atopic eczema	Intervention: Borage oil Two 500mg capsules twice daily (460mg of γ linoleic acid) Comparison:	Follow up period: 12 weeks Outcome measures: Effectiveness SASSAD Score Visual analogue scale for severity of itching,	Adult and children data were analysed together. Authors state that subset analysis of adults and children yielded no suggestion of any differences in results from the combined data Effectiveness: SASSAD & symptom	Gamma linolenic acid is not beneficial in atopic eczema	Good quality RCT No individual reporting of children's data

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
		withdrew during trial		Olive oil same regimen	sleep, disturbance and irritability Children/parents overall assessment of response to treatment (5 point scale) & overall tolerability of treatment (4 point scale) Need for topical corticosteroid (five point scale) Safety Monitoring of adverse events by non-leading questions at each visit. Children were assessed at 2,4,8 & 12 weeks	scores fell (improved) in both groups with a marginally greater improvement in the placebo group No statistically significant differences in overall assessments of response or tolerability between the groups. No differences in topical steroid use between the groups (no statistics used) Safety: Adverse event profile was similar in both groups. Adult & children's data reported combined Adverse events reported were: Upper respiratory tract infection; diarrhoea; nausea & vomiting; abdominal pain; asthma; allergic rhinitis; urticaria; new rash; muscular skeletal pains; skin sepsis; glandular fever headache		
Perharic L; Shaw D; 1992 [477]	Study Type: Case report Evidence level: 3	n=9	Of the nine adult cases, n=4 were being treated for atopic eczema , n=4 psoriasis and n=1 ichtyosiform erythroderma	Four cases of atopic eczema patients after 3 weeks to 10 months treatment with CHM showed clinical symptoms of : Case 1: unwell, jaundice, fulminant liver failure. Case 2:	Case1: fatal outcome Case 2: liver function returned to normal within 3 months of stopping CHM. Case 3: liver function returned to normal within 5 weeks. Case 4: Liver enzyme levels were checked.			Suggested causative agents: licorice and skullcap (Scutellaria spp)

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				shivering fatigue, general ill health. Case 3: flu like illness, ear infection Case 4: none				
Lord GM; Tagore R; 1999 [479]	Study type: Case report Evidence level =3	n=2	Case 1: 49 year old white woman with a history of atopic eczema Case 2: 57 year old woman with with 'chronic eczema.'	Case 1: presented at GP with headaches and hypertension. Only medication was a Chinese herbal remedy taken for past 2 years. Case 2: Admitted to hospital with end stage renal failure History of anorexia, lethargy and nausea. Had been taking 'Chinese herbal tea' for 6 years.	Case 1: Creatinine levels 662µmol/L and urea 35.7mmol/L 'Substantial proteinuria' Echogenic kidneys which progressed rapidly to end stage renal failure followed by renal transplant. Case 2: creatinine 841µmol/L, urea 20.6 mmol/L Ultrasound revealed reduced renal cortical thickness. Haemodialysis as started and patient placed on the transplant list.			The causative agents of these case reports was thought to be aristolochic acid (nephrotoxin). It was found in both Chinese herbal preparations

Behavioural therapies

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Hampel P; Rudolph H; Petermann F; Stachow R; 2001 496	Study Type: Cohort Evidence level: 2-	n= 60 in total n= 44 at follow up assessment of which n=25 for the experimental group, n=19 for the control group	Children with a mean age of 12.64 years (n=44) diagnosed with atopic eczema (mean SCORAD 37.9 SD 15.54 (n=60))	Intervention: Cognitive-behavioral based stress management training 10 one hour training sessions 4 sessions standard patient education regime according to German guidelines 6 sessions of 'anti-stress training' Comparison: Standard patient education program 6 sessions	Follow-up period: 6 months Outcome Measures: SCORAD index for severity of disease German Coping questionnaire (Stressverarbeitungsfragebogen SVF-KJ) performed at time 0,1month, 6 months	Immediately after treatment (1 month) both groups showed a significant reduction in disease severity ($p<0.001$) regarding the SCORAD index. At 6 months, the cognitive-behavioural stress management training led to improvements in subjective health status (post hoc analysis) and the ability to cope with common stressors	Study is EL= 2- as it is a non-randomised controlled study, with large dropout at 6 months. Post hoc analysis. Language, quality of write up and statistical presentation difficult to interpret. The funding of the study is unknown

Education and adherence to therapy

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Reviewer comments
Staab D;Diepgen TL;Fartasch M;Kupfer J;Lob-Corzilius T;Ring J;Scheewe S;Scheidt R;Schmid-Ott G;Schnopp C;Szczepanski R;Werfel T;Wittenmeier M;Wahn U;Gieler U; 2006 Apr 22 498	Study Type: RCT Evidence level: 1-	992 randomised (823 analysed) Education group, n=446 Control group, n=377	Children with atopic eczema aged 3months-7 years (n=274) and 8-12 years (n=102), adolescents with atopic eczema aged 13-18yrs (n=70), and controls (n=244, n=83, and n=50 respectively). Mean SCORAD score at baseline was 42-43 (objective SCORAD ~33-34).	Intervention: 2-hour group sessions of standardised education programmes for atopic eczema once weekly for 6 weeks. The programme was tailored to age groups (3months - 7 years, 8-12 years, 13-18 years). Education covered medical, nutritional, and psychological issues and were carried out by a multiprofessional team of dermatologists or paediatricians, psychologists, and dieticians who had undergone a 40-hour training programme. Comparison: No education	Follow-up period: 1 year Outcome Measures: 1) Severity of eczema (SCORAD) 2) Subjective severity (Skin Detectives questionnaire). 3) Quality of life for parents of affected children aged less than 13yrs* 4) Itch questionnaires, in children 8-12 years (measuring itch and behaviour using JUCKKI and JUCKJU)	1) Between group difference in total SCORAD scores (95% CI) Age 3 months to 7 years, -5.2 (-8.2 to -2.2), p=0.0002 Age 8-12 years, -8.2 (-13.6 to -2.8), p=0.003 2) Between group differences in subjective severity scores (95% CI) Age 3 months to 7 years, -1.1 (-1.9 to -0.3), p<0.001 Age 9-12 years, -2.1 (-3.4 to -0.8) 3) Parents of affected children aged less than 7 yearrs experienced significantly better improvement in all five quality of life subscales, whereas parents of children aged 8-12 yrs experienced significantly better improvement in 3 of 5 quality of life subscales (confidence in treatment, emotional coping, acceptance of disease) 4) Improvement in the itching behaviour of children who received education vs those who did not for subscales 'catastrophisation' (negative thoughts of pain that have got out of control): 0.7, 95% CI –8.9 to –5.1 versus –1.8, 95% CI –3.5 to –0.2: p< 0.0001, and coping 1.0, 95% CI –0.3 to 2.3 versus –0.4, 95% CI –1.6 to 0.8: p<0.05. No further details	Funding: German Federal Ministry of Health and Social Services. The study was open-label. [EL=1-] because 17% were lost to follow-up and were not included in the analysis of results (10% from intervention group, 24% from control group). *QOL measured using 'the German questionnaire "quality of life in parents of children with atopic dermatitis"'. This scale consists of 26 items divided into 5 subscales; psychosomatic well being, effects on social life, confidence in medical treatment, emotional coping and acceptance of the disease.
Broberg A;Kalimo K;Lindblad	Study Type: RCT	50 randomised, 42 analysed	Girls (n=24) and boys (n=26)	Intervention: Routine	Follow-up period: 4 months	1. % reduction in eczema score (nurse education vs control)	Funding: none declared.

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B;Swanbeck G; 1990 499	Evidence level: 1-	nurse-delivered education n=23 'routine' information n=19	aged 4 months to 6 years and 2 months, enrolled from the out patient clinic. All had atopic eczema (AE) of varying severity, diagnosed based on the criteria of Hanifin and Rajka.	information on eczema given by the physician during medical visits plus time spent with a trained nurse to receive further information on eczema treatment and practical training in controlling AE Children in both groups were also prescribed emoillents, topical hydrocortisone and when indicated also topical triamcinolone with or without combination with topical antimycotics, systemic antibiotics and antihistamines Comparison: Routine information on eczema given by the physician during medical visits	Outcome Measures: 1. Total eczema score based on type, intensity and distribution of lesions where Intensity graded from 0-4 and erythema, lichenification, vesiculation, excoriation, papules and dryness were scored seperately as follows: 0-no symptoms 1-mild 2-moderate 3-marked 4-severe Distribution was graded from 0 to 4 as follows: 0-no eczema 1-one local site affected 2-two local sites affected 3 three local sites affected 4- four or more local sites affected. Then the intensity score for each kind of lesion was further multiplied by the by the distribution score. The maximum score was was 96. Itch was evaluated from 0 to 4: 0- no itch 1- mild itch not disturbing play or sleep 2- moderate itch not disturbing play or sleep 3- marked itch disturbing play or sleep 4- severe itch disturbing play or sleep. 2. Quantity of topical hydrocortisone used (strength	-78% vs -62%, p<0.05. % reduction in distribution score: -52% vs 40%, p=NS % reduction in itch score -56% vs -30%, p=NS 2. Children in the nurse education group used significantly more hydrocortisone (quantities not stated), p<0.01.	[EL=1-] because inadequate information on randomisation techniques, no sample size calculation and information on statistical analysis inadequate. Fewer analysed than randomised. Nurse education programme: 2-hour session covering general information about AE, environmental control, topical treatments (type and how to use), practical advice to aid self-management, importance of maintenance therapy, expectations.

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					not stated)		
Staab D;von RU;Kehrt R;Erhart M;Wenninger K;Kamtsiuris P;Wahn U; 2002 Apr 101	Study Type: RCT Evidence level:	204 (145 followed to 1 year)	Children aged between 5 months-12 yrs with moderate-severe AD for at least 4 months, and diagnosis confirmed by a physician according to the (SCORAD score>20 points). Diagnosis made according to the clinical criteria of [Hanifin and Rajka]	Intervention: Inter-disciplinary, structured educational program which covered medical, nutritional, and psychological issues in 6 group sessions of 2 hours each Comparison: No intervention (delayed intervention - would participate in the training programme 1 year later	Follow-up period: 1 year Outcome Measures: 1) Severity of eczema (SCORAD) 2) Treatment habits 3) Quality of life 4) Treatment costs	1) mean decrease in severity score (SCORAD) -20 points VS -16 points (p=0.43) 2) 82% vs 67% still used regular skin care (p=0.041) 65% vs 38% used topical corticosteroids, p=0.001. 30% vs 0% reduction in % seeking 'unconventional' (alternative) help for their condition 67% vs 40% maintained dietary restrictions 22% vs 8% had removed a pet from their household because of atopic eczema p= 0.019 3) In the disease specific health related QoL questionnaire there was a trend towards a greater increase in the education group regarding confidence in medical treatment as compared to the control group (p =0.016) 4) Treatment costs- after a yr, cost reduction was also seen to to have decreased more in the intervention group compared with the control.[119 versus 65; p= 0.043]	
Grillo M, Gassner L, Marshman G et al 2006 500	Study Type: RCT Evidence level: 1+	61 Educational intervention, n=32 Control, n=29 Exclusions: severe eczema requiring	Children aged 0-16 years diagnosed with atopic eczema; 35 boys, 26 girls, mean age 4.3 years (range 4 months to 13 years). 70.5% reported more than three flares per month. 34% used one topical corticosteroid, 26% used two different topical corticosteroids (one	Intervention: A 2-hour workshop together with their usual management regimen. Education covered: understanding the condition, trigger factors, investigations, basic skin care,	Follow-up period: 12 weeks Outcome Measures: 1) Severity (SCORAD) 2) DFI 3) CDLQI 4) IDQOL	1) Change in score -54% education vs -16% control, p<0.005 2) Change in score -33% vs -27%, p=NS 3) Change in score -78% vs 27%, p=0.0004 4) Change in score -37% vs -38%, p=NS	Funding: partially by Flinders Medical Center Volunteer Study Award Three children lost to follow-up but their data were included in the analysis of results.

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		treatment with systemic immunosuppressants.	for face and one for body). 27.9% preferred not to use topical corticosteroids even when the eczema was moderate to severe. Basline SCORAD score 50.97 education group vs 47.73 control; DFI 11.09 vs 10.86; CDLQI 8.1 vs 9.69; IDQOL 11 vs 8.63	topical corticosteroid therapy, infection, wet wraps, additional treatments, complementary therapies. The intervention included a practical session on wet wrapping and cream application. Time for questions and for sharing ideas and experiences was provided. Comparison: Usual management			

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Ricci G;Bendandi B;Aiazzi R;Patrizi A;Masi M; 2004 88	Study Type: Other Evidence Level: 3	Intervention: Six 2-hour group sessions, conducted at weekly intervals covering medical, psychological and behavioural issues of atopic eczema, which were epidemiology, diagnostic tests, nutritional aspects, development of inhalant allergy, prevention, treatment of symptoms. Comparison: N/A	Families of 17 children with atopic eczema	Families of 17 children with atopic dermatitis(AD), [16 Caucasians and 1 Afro-caucasian], mean age 18 months (range 5-48 months).	Satisfaction (questionnaire), completed by 14 families	79% of the families thought the programme was satisfactory Their attitudes towards the disease was reported as 'tranquil' in 79%. Improvements in relations with the child were reported in 11 families, and in communication with partner in 50%. Less frequent itching was in child was reported in 4 families (30%) and 43% benefited from a more stable sleeping-waking rhythm.	Funding: none declared Aim of the study was to inform families of children with AD about the natural courses of the disease, to improve their management of AD and to offer them the opportunity of a more open and wide medical dialogue.
Cork MJ;Britton J;Butler L;Young S;Murphy R;Keohane SG; 2003 Sep 504	Study Type: Other Evidence Level: 3	Intervention: A 30 min conversation with a dermatologist and specialist dermatologist nurse that involved listening and explaining the nature of atopic eczema . -Followed by a full skin examination according (done according to the guidelines for treatment of atopic eczema according to the British association of dermatologists) - diagrammatic explanations to patients on the causes of eczema and how it's treatment exert their effect (emollients, wet wraps and topical steroids) - Problem of non-specific irritation to	51	51 children (new patients) with atopic eczema referred to one dermatologist because they had uncontrollable eczema. Mean age 4 year 4 months, range 2 weeks to 14 years. Mean SASSAD score 42.9. The interval between the intervention and follow up final visit varied for each child; the average interval was not reported.	1) Control/ improvement of the eczem using the SASSAD score 2) Parent's assessment of child's itching, sleeping and and irritability (using a 10-cm visual analogue scale) 3) Use of emollients 4) Use of topical corticosteroids 5) Use of wet wraps	1) The mean SASSAD score fell from 42.9 to 4.6. 2) Parent assessment of eczema severity fell: Itching from a mean 5.6 to 0.4 Irritability from 5.3 to 0.3. 3) The total quantity of emollient used increased form 150g weekly to 581g. At the second and subsequent visits 95% of the children were being treated with 3 types of emollients cream/ointment, bath oil substitute. The proportion of children whose eczema was controlled (SASSAD< 5) with emollients alone rose from 0 at visit one to 12% at visit 2 and 22% at visit 3. A Spearman's test showed a significant reduction in SASSAD with increasing quantity of emollient.	Funding: no external funding received. This was not a RCT and the study design can not show a direct link between education and adherence to treatment. The education programme consisted of: First visit – seen by dermatologist and specialist nurse for at least 40 minutes, 30 minutes spent listening and explaining the nature of eczema. Full skin examination. Nurse demonstrated use of prescribed products and gave written instructions. Contact details for clinic given in event of emergency. Follow-up visit at 3 weeks, when questionnaire repeated, and third visit after 6-8 weeks.

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		any topical product when eczema is severe -Explanation of the role of selected emoillents, steroids and dressings - targets for the estimated length of time a tube or tub of the emollients and steroids should last _ demonstration on how to apply each product by a the nurse and repeat of how long each one should last. -Advice to help make the treatment more acceptable to children suchas warming of emollients cream/ointment in a sink of warm water prior to application. -written instructions gi				4) At over four visits there was a decrease in the use of very potent, potent and moderate steroids and the use of mild steroids. 5) The use of wet wraps intermittently was seen to increase from 7.8% to 33% by visit 4.	
Charman CR;Morris AD;Williams HC; 2000 May 503	Study Type: Other Evidence Level: 3	Intervention: Survey about concerns over steroid treatment Comparison:	142 parents of children (aged < 16) 58 adults (aged > 16)	Children and adults with atopic eczema. Mean age 13 years, (median age 5.4 years, range 4 months to 67.8 years)		104/142 (73.2%) of parents (of children <16 years old) were worried about using steroid creams and ointments on their child's skin 35/104 (36.5%) of the parents who had worries about steroid creams, the worries stopped them from using the steroids prescribed by a doctor. Patients age, gender, duration of eczema or outpatients status (new or follow up) had no effect on whether they worried about using topical corticosteroids or if the worries stopped the used of the	Funding: Author funded by a Health Services Research Training Fellowship from Trent NHS Executive. Views only the study can not show a direct link between views and adherence

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						topical corticosteroids. The reasons given for fears about using topical corticosteroids (adults and children): skin thinning (34.5%), non-specific tong-term effects (24%), absorption/effects on growth and development (9.5), ageing/wrinkling (3.5%), changes in skin colour (3%), makes eczema worse (3%), may become immune to effect (3%), may become dependent (2.5%), scarring (2%), stretch marks (1%), pain/stinging (1%), reduced immunity to infections (0.5%), cataracts (0.5%), cancer (0.5%), sunburn (0.5%), bruising (0.5%), increased body hair (0.5%).	
Fischer G; 1996 May [502]	Study Type: Other Evidence Level: 3	Intervention: Attitude survey asking: 'Cortisone creams are dangerous' 'Cortisone creams should only by used for severe eczema' 'Cortisone creams are too dangerous to use on my child' 'Have you been told that cortisone creams are dangerous?' By whom 'I would prefer to use natural therapy' 'I think my child's problem is due to allergy' 'Do any treatments sting or itch?' Which? 'My child is unco-operative with treatment'	109	Parents of children answered a Attitude survey. Children were aged 1 month to 10 years with atopic eczema presenting as new patients at an outpatient's clinic.		'Cortisone creams are dangerous' 40% yes 20% no 40% don't know 'Cortisone creams should only by used for severe eczema' 57% Yes 14% No 29% Don't know 'Cortisone creams are too dangerous to use on my child' 20% Yes 47% No 33% Don't know 'Have you been told that cortisone creams are dangerous?' 64% Yes 36% No By whom	Funding: none declared. These are just the view of one group of parents one areas of Australia in 1995, it may not reflect the view of parents now in the UK. Views only the study can not show a direct link between views and adherence

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		'Treatment is too time consuming' 'Treatment failed because the condition returned after it was stopped' 'Treatment is too expensive' 'I spend per month on treatment' Comparison:				33% Friends 28% Family 22% GP 10% Pharmacist 4% Dermatologist 'I would prefer to use natural therapy' 46% Yes 17% No 37% Don't know 'I think my child's problem is due to allergy' 34% Yes 27% No 39% Don't know 'Do any treatments sting or itch?' 64% Yes 36% No Which? 75% Sorbolene 5% Pinetarsol 5% Bath oil 10% Cortisone cream 'My child is unco-operative with treatment' 34% never 49% sometimes 15% always 2% only on the face 'Treatment is too time consuming' 48% never 13% rarely 32% sometimes	

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						7% always 'Treatment failed because the condition returned after it was stopped' 54% Yes 46% No 'Treatment is too expensive' 54% Yes 25% No 21% Don't know 'I spend per month on treatment' 35% <$10 24% $11-20 16% $21-30 25% >$30	
Ohya Y;Williams H;Steptoe A;Saito H;Iikura Y;Anderson R;Akasawa A; 2001 Oct 505	Study Type: Other Evidence Level: 3	Intervention: A cross-sectional survey of mothers of children with atopic eczema asked about the adherence to different components of atopic eczema care by the parent and the child. Comparison:	205	Mothers of children with atopic eczema. Children aged 0 to 19 years (mean 6.9 +/- 4.9 years)		Adherence measures Removal of carpets: not eliminated by 17% Cleaning rooms every day: No 21% Using antimite bedding for child: No 24%, partially 18% Using antimite bedding for family: No 31%, partially 21% Bating every morning: less than once a week 32%, a few days a week 21%, every day 47% Using ointment every morning: less than once a week 13%, a few days a week 17%, every day 70% Frequency of ointment use during the day: once a day 19%, twice daily but advised three times 20%, twice daily as advised 36%, three times daily as advised 25% Demographic items, steroid phobia, and depression correlation with	Funding: Educational grant from Pfizer Health Research Foundation. Study was carried out in Japan, unknown if an UK population would be the same or similar. Advice given focuses on daily repeated skin-care treatment and house dust mite allergen reduction measures. 90% of study participants had visited the clinic at least three times previously.

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						adherence measured using one way ANOVER: Adherence to mite avoidance the child with atopic eczema also had asthma 2.8 +/- 1.5 compared to those without 2.2 +/-1.7, p < 0.05 Age, sex and duration of follow up did not predict adherence No difference in adherence to mite avoidance when looking at frequency of visiting clinic, number of siblings, anxiety about steroids, steroid use or depression in parent Adherence to skin care treatment in children who visited biweekly or more 5.3 +/-1.9 compared to bimonthly or less 3.3+/- 2.1, p < 0.05 Adherence to skin care treatment in children who used steroids every day 4.8 +/- 2.2 compare to not used 3.5+/- 2.7, p < 0.05 No difference in adherence to skin care treatment when looking at if the child also had asthma, number of siblings, anxiety about steroids or depression in parent Psychosocial factors correlation with adherence measured using bivariate correlation: Association with skin-care adherence The doctor patient relationship: 0.368, p < 0.01 Self-efficacy in management: 0.167, p < 0.05 Spouse cooperation: 0.198, p<	

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						0.01 Resentful child attitude: -0.058, p > 0.05 Concerns about cost: -0.050, p > 0.05 Bathing reluctance: 0.033, p > 0.05 Late awake: -0.002, p > 0.05 Social support: 0.229, p < 0.01 Maternal worry about child's eczema: 0.196, p < 0.01 Victimized feeling: - 0.023, p > 0.05 Perceived severity of eczema: 0.270, p < 0.01 Association with mite avoidance. The doctor patient relationship: 0.145, p > 0.05 Self-efficacy in management: 0.025, p > 0.05 Spouse cooperation: -0.038, p > 0.05 Resentful child attitude: 0.192, p < 0.05 Concerns about cost: -0.039, p > 0.05 Bathing reluctance: -0.248, p < 0.01 Late awake: 0.226, p < 0.01 Social support: 0.056, p > 0.05 Maternal worry about child's eczema: 0.171, p < 0.01 Victimized feeling: 0.164, p < 0.05 Perceived severity of eczema: 0.267, p < 0.01	

Monitoring growth

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Kristmundsdottir F;David TJ; 1987 Jan 510	Study Type: Case series Evidence Level: 3	n=89 children	Children with atopic eczema of duration of at least 1 year who had at least 5% of skin surface affected and who had been referred to a paediatrician or dermatologist because of the severity of their condition. 55 boys (mean age 5.35, range 1.3-16.95 years. 34 girls (mean age 5.2, range 1.66-10.85 years)	Intervention: None Comparison: None	Height SD Sitting height SD Subischial leg length SD Weight Triceps and subscapular skinfold tests Head circumference SD Skeletal maturation using the TW2 method SD	10% of the 89 children had a standing height below the third centile (7 were boys and 2 were girls). n=6 were >2SD below mean n=3 were more than 2.5SD below mean Mean height was less than the general population although the overall distribution was not statistically significantly different Male -0.31 SD1.22 Female -0.37 SD1.11 Both boys and girls had statistically significantly reduced sitting height (p<0.001) Subischial leg length was not different from normal standards. The difference between sitting height and subischial leg length was disproportionally shorter than normal standards (mean values, boys 0.55SD, girls 0.88SD The centile distributions for weight and skinfold tests were not different from the normal population The mean head circumference was significantly greater than for the general population for both boys (p<0.01) and girls (p<0.02). Skeletal maturity SDS was more delayed in the girls (p<0.001) than the boys (p<0.05) Using parental heights (n=69), there was a	This study suggests that impaired linear growth is a feature of atopic eczema and that caution in the use of potent TCS in children should be applied.	This study includes a highly selected population with severe atopic eczema. The funding of this study is undeclared

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						small but statistically significant excess of boys over girls with a corrected height centile below the 10th centile (10 vs. 5). There were consistent trends of disease severity, TCS strength and asthma score with decreasing height centile.		
Pike MG; 1989 509	Study Type: Cohort Evidence level: 2-	n= 128 parents of children with atopic eczema n=117 parents of healthy control children	Children with atopic eczema who had been seen by a hospital consultant (no details of severity) Mean age 6.9 years (range 1.2-16.2 years) 50% were boys Control children mean age 7.0 years (range 1.1-16.5 years). 52% were boys	Intervention: None Comparison: Growth between children with atopic eczema and unaffected children	Follow-up period: None Outcome Measures: Postal questionnaire: Envelope contained two envelopes. One contained a questionnaire concerning the child with eczema. The second, a questionnaire for a healthy similarly aged child known to the family. The questionnaire included questions on: Paternal employment presence or absence of asthma date of birth and height of both parent and child (instructions were given as to height measurement) If there was no response a second letter was sent	245/296 replies were received (83%) 128 cases and 117 controls Not all questionnaires were complete There were no significant differences in ages, paternal employment (measure of social class) and parental height of both sexes between the two groups. The mean SD score of the children with eczema (-0.4505 SE 0.119) was significantly less than the controls (-0.0595 SE 0.097) even after controlling for parental height ($p<0.005$) n=12 were more than 2SD below the mean, n=4 were more than 3SD below the mean (12 of these very short children had asthma) 57% of the children reported no asthma or use of antihistamine or steroid treatment. When compared to the control group who also answered negatively, the height SD was significantly different ($p<0.01$) even after correction for age and parental height. There was also a significant difference even when children under 5 years were excluded (the rationale that the onset of asthma is later; $p<0.005$)	The findings of this study suggest that children who have atopic eczema but not asthma are shorter than genetically expected from parental height.	The study was funded jointly by the National Eczema Society and the Glaxo group Research Ltd.
Massarano AA;	Study Type: Case series	Intervention: None	n=68 children	Children aged 2.3-11.9 years (mean	Height SD of parents and children	Highly significant correlation (Spearman coefficient) between height SD score and	This study suggests that children with atopic	The funding of this study is

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1993 512	Evidence Level: 3	Comparison: None		6.2) years with atopic eczema diagnosed by the Hannifin and Rajka criteria who attended a university department of child health. The median surface area affected by eczema was 30% (46 boys and girls)	Maximum figure ever recorded for surface area of skin affected by eczema TCS and SCS use Exclusion diets were noted Bone age was measured in children above 6 years Presence of asthma was reported and graded	surface area of eczema r_s=0.42, p=0.03 The children were then divided into two groups for analysis: I) less than 50% skin involved n=41 II) more than 50% skin involved n=27 age and sex ratios were similar group II had higher treatment (p<0.01) and diet (p<0.0001) score but were similar for asthma The height SD of group I children was comparable to their parents. Only n=2 were below the third centile (of these ?missing number eczema lesions were inflamed) The height SD of the group II children was significantly different from their parents (p=0.001) and the children in group I (p=0.0007) n=8 were below the third centile. 4/8 were receiving a elemental diet and 1/8 had received systemic steroids The bone age of children over 6 years was mildly retarded in both groups but the difference was not statistically significant (U=225 p=0.09) Predicted heights of group 2 children were not significantly below those of mid-parental height (p=0.08) but were below those of Group I despite having taller parents (U=111,p=0.18) Regression analysis showed that the height SD scores were best explained by parental target height (r_2=0.24) Surface area of eczema r_2=0.13 Combination of above explained 36% of variation in height	eczema which affects less than 50% of their skin surface area have normal height. Those with more extensive disease may have impaired growth for which the mechanism is unknown.	undeclared. Growth of children is related to surface area of skin affected as opposed to severity

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						Further combination with treatment and diet only had a marginal effect (r_2=0.03, r2=0.0 respectively) Asthma and duration of disease had no effect.		
Morava E; 1994 [513]	Study Type: Case series Evidence Level: 3	Intervention: None Comparison: None	n=92 of which n=72 had atopic eczema, n=12 had atopic eczema and asthma and n=8 had urticaria	n=92 children (51 boys and 41 girls) age range 0.51-10.5 years for boys, 0.51-9.5 for girls Allergic status was confirmed by IgE levels and a detailed medical history concerning their atopic status was taken.	Somatometric measurements: Skinfold thickness (Tanner-Whitehouse) BMI (French) Relative body weight 120% =obese Height SD score >2.0=obese	Children were divided into 2 age groups: Group 1 age 0-2.99 years n=36, Group 2: age 3 years upwards n=56 Group 1(&2): Children were tall and heavy for age 16/36 (25/56) were above the 75th weight centile 11/36 (20/56) were above the 90th weight centile. 14/36 (21/56) were above the 90th height centile skinfold tests: 3/36(20/56) had tricep folds above the 90th centile 6/36 (20/56)had subscapular skinfold thickness above the 90th centile but 6/36 (N/A) were also under the 10th centile for both these measures BMI: 4/36 (16/56) were above the 90th centile 10/36 (N/A) were below the 10th centile Relative weight: above 120% in 4/36 (17/56)cases 7/36 (20/56) were above 90th centile for weight for height Mean SD score was 0.43+/-0.15 (N/A) 5/36 (N/A) had an SD of >2. Sub group analysis for group 2 in which 8/56 had urticaria and 12/56 had atopic eczema and asthma showed these above measurements	The study shows that in this population of atopic children, there is a special pattern of somatic development characterised by high stature and a high ratio of obesity in the prepubertal group	The funding of the study is undeclared. Population is Hungarian children for whom obesity patterns may be different from UK children. Hungarian centile charts were not available for some of the measures

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						were similar in all three groups		
Patel L; 1998 508	Study Type: Cohort Evidence level: 2-	n=77children with atopic eczema n= 71 children acting as controls	Children with atopic eczema (mean age 4.8 years, range 2.0-10.5 years) attending a university department referred by paediatricians or dermatologists because of the severity or intractable nature of the atopic eczema. Children had mild to severe atopic eczema involving 8-95% (median 47%) of the body surface area	Intervention: None Comparison: Linear growth between prepubertal children with atopic eczema and those whom were unaffected	Follow-up period: 2 years Outcome Measures: For children with atopic eczema: Age of onset Percentage body surface affected Potency of TCS Asthma scores For both groups: Height velocity at year 1 and 2 Weight (BMI) SDS were calculated of the above triceps and subscapular skinfold Bone age by wrist radiographs	Height and height velocity SDS did not differ between patients and controls and were not influenced by body surface area affected by atopic eczema, TCS potency or coexisting asthma. Height SDS (r =-0.37), and height velocity SDS (r=-0.31) correlated inversely to age in patients but not in controls. A greater proportion (z=2.84) of patients than controls had year 2 height velocity SDS of less than -1.96. Patients had a mean delay in bone age of 0.22 years and 0.41 years at year 1 and year 2 of the study respectively. The delay in bone age correlated positively with age (r=0.39) and duration of atopic eczema (r=0.39)and negatively with height SDS (r=-0.5) and height velocity SDS (r=-0.38)	This study shows that prepubertal children with atopic dermatitis are not as tall as controls. However, as they approach puberty, their height velocity decreases, the proportion of children with extremely low height velocity increases and the delay in bone age increases. These features are consistent with a pattern of growth seen in people with constitutional growth delay.	The funding of this study is undeclared
Patel L;Clayton PE;Jenney ME;Ferguson JE;David TJ; 1997 Jun 511	Study Type: Cross sectional Evidence level: 3	n=35 adult patients with atopic eczema n=35 control patients with contact dermatitis or psoriasis	Adult patients (mean age 26.3 years, range 18-50 years) 15 men and 20 women with a history of childhood onset eczema before the age of 5 years, continuing throughout childhood and requiring attendance at a hospital dermatology clinic. Control group adult patients (mean age 31.6 years, range 18-46 years) 15 men and 20 women attending	Intervention: None Comparison: None	Follow-up period: None Outcome Measures: Age of onset of atopic eczema Age when TCS started and the potency of the TCS Duration of treatment Surface area affected History and treatment of asthma Standing and sitting	There were no significant difference of standing height, mid parental height, sitting height and subischial leg length SD values and BMI between the atopic eczema and control group or any sub analysis thereof: surface skin affected, potency of TCS, with or without asthma	This study shows that short stature was not a feature of this group of adult patients who had childhood onset atopic eczema continuing into adulthood, severe enough to require specialist care. This suggests that if growth impairment occurs in childhood atopic eczema, it is likely to be temporary and reversible.	The funding of this study is undeclared

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			dermatology clinic with no history of atopy.		height Parental height if known Weight SD values were calculated for the above as well as the BMI			
Ellison JA; 514	Study Type: Case series Evidence Level: 3	Intervention: None Comparison: None	n=70 male and 40 female patients with atopic eczema	Patients had developed atopic eczema in early childhood (median age of onset 0.7 years, range 0.01-5.0 years) and had the condition throughout growth measurement period. 92/110 also had a history of asthma which was mild in 85 of cases	Height Weight BMI expressed as SDS	Regression analysis showed that the trends in height, weight and BMI SDS for atopic eczema patients were significantly different from zero and also different between males and females. Both sexes were short and relatively overweight from early childhood and the trend was more pronounced in males than females. At 5 years (school entry) the 50th centile BMI of male but not female was 0.44kgm-2 higher than the reference population but height and weight were lower. The age at adiposity rebound in atopic eczema males and females were 0.8 years and 0.7 years later than in the UK population (5.4 years, 5.3 years, and 6.2 years respectively). Children with atopic eczema attained peak height velocity later than the 1990 UK population (males 16.0 years vs. 13.5 years, p=0.0002; females 13.4 years vs.11.0 years p=0.008). In addition males had a greater mean gain in height during late adolescence (12.2 vs. 8.8cm, p=0.03) and were shorter as young adults (170.9 vs.177.6cm, p=0.0005).	This study showed that patients with childhood onset atopic eczema were relatively overweight very early but had a later adiposity rebound, were short in childhood and had a delayed adolescent growth spurt. The authors suggest that serial growth measurements should be done on all children with troublesome atopic eczema and can be helpful in counselling about the growth prognosis	The funding of the study is undeclared
Carrington LJ; 2006 515	Study Type: Case series Evidence Level: 3	Intervention: None Comparison: None	n=256 7-year old children	7-year old children registered with 2 GP practices in Northampton UK	Historical and current growth data obtained through a structured interview either at surgery or home. 3 part questionnaire collecting demographic data, history of illness and	Atopic eczema at 7 years was not related to any anthropometric indices at birth or during infancy. A smaller head circumference at 10-15 days of age was noted in children with current wheeze at age 7 years (p=0.018) regardless of confounding factors. Comparison of children with a head circumference over 36.5 cm at 10-15 days with those under 36.5 cm showed reduced odds for wheeze at 7 years (odds ratio 0.12, 95% CI 0.03-0.44, p trend=0.009)	Atopic eczema at 7 years of age is not related to any growth data from birth or during infancy.	The study was funded by the Northampton NHS Primary Care Trust

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					growth measurement both current and historical. Demographic data: occupation (used for social class), number of people in house, pets, smoking and immunisation history. History of illness: data on wheezing and eczema were collected on questions based on the International Study of Asthma and Allergies in Childhood (ISAAC) criteria Growth data: were obtained from PCRB plus current measurements by health visitor.			
Fergusson DM;Crane J;Beasley R;Horwood LJ; 1997 Dec 516	Study Type: Case series Evidence Level: 3	Intervention: None Comparison: None	n=891 children who had complete data on patterns of atopic illness up to the age of 16 years (original cohort n=1265 children)	A birth cohort of 1265 New Zealand children	Perinatal measures: Birth weight gestational age head circumference length at birth Measures of atopic illness up to 16 years by structured interview and hospital, GP and parents records including eczema and asthma Two categories of	There was no association of eczema or any other atopic status other than asthma with perinatal measures as shown by Chi square tests. Exception to this was a small non- significant association between birth weight and other atopic status as defined using the criterion of at least one medical attendance ($p<0.05$) There were significant associations between head circumference and risks of asthma (Any diagnosis of asthma $p<0.1$, 5+ medical consultations for asthma $p<0.0001$). A head circumference of greater than 37 cm had greater risks of asthma.	Large head circumference at birth may be associated with the development of asthma but no other atopic condition.	The study was funded by the Health Research Council of New Zealand, the National Child Health Research Foundation and the Canterbury Medical research Foundation.

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					atopic eczema were used i) any eczema : whether the child had made any medical consultation for eczema by the age of 16 years: 36.6% of the sample met this criterion, ii) Recurrent eczema: whether the child had made at least three medical consultation for eczema by the age of 16 years: 13.6% of the sample met this criterion	Even after allowing for confounding factors e.g. Maternal smoking, maternal drinking, gender, birth order etc children with a head circumference at birth of 37cm or greater had odds of asthma that were 1.8 ($p<0.01$) to 3.0 ($p<0.0001$) times higher than the these with head circumference of 37cm.		
Eichenfield L; Ellis C; Fivensen D; Herbert A; Dromgoole S; Piacquadio D. 2007 517	Study Type: Case series Evidence Level: 2-	n=21	'Healthy' boy and girls in equal numbers with 'stable atopic eczema' mean age 9+/-2.5 (range 5-12) years. No systematic or topical treatments exclusive of emollients were allowed for 2 weeks prior to study.	Intervention: Lipid-rich moisturising formulation of hydrocortisone butyrate 0.1% three times over a minimum body surface area of 25% daily for up to 4 weeks. In children noted to be 'clear' at 3 weeks, treatment was discontinued early. Comparison: none	Evaluations were made at days 1, 8, 15, 22 and 29. PGA for overall disease severity (0=clear to 6=extreme) Four point scoring system for severity of individual symptoms (0=none to 4=severe) Pruritus severity scores were defined by interference with daily activities % BSA Cosyntropin® stimulation test	20/21children completed the study. 2/22 children were clear at 22 days and 18/22 were treated for the 4 weeks. PGA scores, pruritus scores, % BSA and individual symptoms severity was improved significantly over the period of treatment. 48% of children were 'clear' or 'almost cleared' at 22 weeks. None of the children were found to have adrenal suppression Mean cortisol conc (µg/dL +/-SD) Day 0: pre stimulation 15.8 (7.0) post stimulation 28.3 (5.5) Final day: pre stimulation 13.0 (4.6), post stimulation 27.8 (4.5). A normal adrenal response was defined as greater than 18ug/dL	Overall a 4 week period with maximal treatment of hydrocortisone butyrate 1% there were no signs of adrenal suppression in 20 healthy children with 'stable atopic eczema'	Small uncontrolled study [EL=2-] This study was funded by a grant from Ferndale laboratories, Inc.

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					(CST) was used to challenge the responsiveness of the adrenal gland with a 30 min post injection assessment at day 1 and end of treatment.	The treatment was well tolerated and no changes in biochemical tests were noted. 2 AE's reported, mild transient burning on 1st day of application and a tinea corporis infection.		
Turpeinen M; [518]	Study Type: Case series Evidence Level: 3	Intervention: Application of hydrocortisone cream 1% followed by skin absorption tests. (n=14) ACTH test at 2 hours to evaluate the effect of previous treatment with TCS. (n=10)	n=18 children of which n=14 had atopic eczema	18 children, (14 with atopic eczema) Aged 6 weeks to 14.4 years with chronic skin disease and who had been admitted to hospital due to the exacerbation of their skin disorder	Serum cortisol determination at 1, 2, 3,4,5,6,8,12,18 and 24 hours after application of hydrocortisone cream Serum cortisol was measured 2 hrs after administration of ACTH bolus,	Endogenous secretion of cortisol was suppressed by dexamethasone. A 24 hour absorption test was performed on 9 children of which 6 showed percutaneous absorption of hydrocortisone cream. The highest serum cortisol level was recorded within the first 6 hours. A 4 hour test was performed on 9 children showed 8 of them had absorbed hydrocortisone. The rise of serum cortisol ranged from 98-2669nmol/L The 2 hour ACTH was performed on 10/14 children with atopic eczema and 3 of these tested had suppressed adrencortical function. This effect was associated with post application of serum cortisol levels following hydrocortisone cream. This occurred more often in infants with severe skin condition than mild or moderate.	The study concluded that this skin absorption test at 4 hours, in addition to the monitoring of adrenocortical function and growth should be recommended for infants with chronic severe skin disorders requiring long term treatment with TCS.	The finding of this study was the Allergy Research Foundation of Finland
McGowan R;Tucker P;Joseph D;Wallace AM;Hughes I;Burrows NP;Ahmed SF; 2003 Sep [331]	Case series EL=3	Intervention: Wet wrap dressings with emollient (n=1) or beclomethasone dipropionate, strength not stated, diluted to 10% (n=6) or 25% (n=1) applied under tubular bandages. Bandages left	8	Children with atopic eczema aged 3.3-8.8 years, median 5.1 years	1) Lower leg length velocity (knemometry); millimetres per week 2) Urinary deoxypyridinoline crosslink excretion (UDPD); median rate, nmol/l	1) 0.42 (vs 0.43 during the pretreatment period), p value not reported 2) 26.3 (vs 25.9 in pretreatment period), p value not reported	This study found no change in growth rates (lower leg velocity) or in urinary excretion of deoxypyridinoline crosslink, a marker of bone turnover, in children treated with wet wrap dressings for a median duration of 12 weeks.	Funding: Addenbrookes Charities Committee, the Marmaduke Shiled Fund, Serono Pharmaceuticals Ltd, and Mason Medical Research Foundation.

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		on for 24 hours a day for up to 2 weeks, reducing to overnight use for 1 week, then as required for the remaining 12 week Comparison: N/A						
Heuck C; 519	Study Type: Case series Evidence Level: 3	Intervention: In period one (run-in of 2 weeks) emollient (Locobase) was given twice daily In period 2 (2 weeks) budesonide cream 0.025% (Preferid) and emollient were applied with an interval of 5 mins morning and night In period three (run-out of 2 weeks) emollient (Locobase) was given twice daily Comparison: None	n=14 children (n=12 completed study)	7 girls and 7 boys with atopic eczema mean age 9.5 years, range 5.8 to 12.5 years were recruited from a secondary centre. There was no treatment 2 weeks prior to study with exogenous glucocorticoids	At time 0, 2 an 4 weeks severity of atopic eczema was scored as to its extent (1-4) and its activity (1-4) Knemometry of the right lower leg was performed twice a week and lower leg growth rates were calculated	Severity of Eczema period 1: 4.33 (2.21) period 2 : 2.78 (1.46)p<0.05 vs.period1 period 3: 2.79 (1.45)p<0.05 vs.period1 Lower Leg Growth period 1: 0.25 (SD 0.43) period 2: 0.14 (SD 0.37) p<0.05 vs.period3 period 3: 0.54 (SD 0.35) p<0.05 vs.period1	The authors suggest that knemometry may be useful for comparing different TCS and treatment regimes in children with atopic eczema	The study is short in duration and small in numbers of participants. The growth measures do not include height and weight (normal growth parameters) The funding of this study is undeclared
Wolthers OD;Heuck C;Ternowitz T;Heickendorff L;Nielsen HK;Frystyk J; 1996	Study Type: Case series Evidence Level: 3	Intervention: In period one (run in of 2 weeks) emollient (Locobase) was given twice daily In period 2 (2	n=13 children	6 girls and 7 boys with atopic eczema recruited from a secondary referral centre. Mean age 9.5 years, range 5.8-12.5 years). Mean body surface	At time 0, 2 and 4 weeks severity of atopic eczema was scored as to its extent (1-4) and its activity (1-4)	Severity of atopic eczema: (Period 1) 1 4.1 SD 2.0 (Period 2) 1.9 SD 1.1 p<0.002 No statistically significant effects were seen on	Type I and II collagen turnover may be suppressed during short term topical budesonide use in children with atopic eczema	The number of the participants was small and the outcome measures of growth were biochemical tests as

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[520]		weeks) budesonide cream 0.025% (Preferid) and emollient were applied with an interval of 5 mins morning and night Comparison: None		area affected 1.1m^2, range 0.7-1.3 No treatment with exogenous glucocorticosteroids in the past year	Serum analysis of IGF-I, IGFBP-3, osteocalcin, PICP, ICTP and PHINP at 2 and 4 weeks	serum levels of IGF-1, IGFFBP-3, osteocalcin or ICTP. The mean (1SD) serum concentrations of PICP and PHINP were reduced between period 1 and 2 PICP 398 (132) and 7.6(1.8) ug/l (p=0.03) PHINP 355(132) and 6.4 (1.4) ug/l (p=0.01)		opposed to clinical measures
Aylett SE; 1992 [521]	Study Type: Case series Evidence Level: 3	Intervention: Beclomethasone dipropionate (BDP) mean dose 1800ug/day in 3 divided doses, range 800-1800. If therapeutic response was judged to be favourable after 4 weeks , the dose of BDP was the gradually reduced over 6 weeks to an maintenance dose for each child Comparison: None	n=15 children of which n=10 provided data for the study	Children with persistent, extensive, non-exudative atopic eczema whose a) condition was not controlled b) age was 2-10 years for girls, 2-11 years for boys c) height above above the 10th centile d) treatment had not included oral, inhaled or nasal corticosteroids in the past year. Mean age of 5.7 years, range 1.8-10.9 years) The median total Ig E was 19,954 kU/l (79-68,300)	At 24 hours and 6 months Plasma cortisol profile and free urinary cortisol Atopic eczema was assessed throughout using standard scores (Pike et al 1989) Weight and height at 0 and 6 months from which height SDS were calculated and were compared to normal values for height (Tanner et al 1966)	14/15 derived benefit from BDP treatment 10/14 were able to reduce to a maintenance dose (mean 1000ug, range 800-1800ug) Of these 10 children: 3/10 continued to grow normally in the 6 months of treatment according to growth charts 7/10 showed some sign of growth impairment (numerical data reported for n=6 only) For this group of n=6: pre treatment median height SDS was +0.285 (95% CI -0.295 to +1.055) Post treatment -0.390(95% CI -0.94 to +0.465) This difference was statistically significant (Wilcoxon Signed Rank Test 0.3-1.03) There was no significant difference in plasma cortisol levels or urinary cortisol excretion although the latter was reduced throughout the study 32.5 (95% CI 26.5-40.00) to 25nmo/24 hour (95% CI 25.0 to 31.5) (95% CI for the difference -3.75-15.0)	Oral BDP is useful in controlling childhood atopic eczema but growth should be monitored regularly through its use.	The data are of use but in the study is small in numbers of children and relatively short term. The funding of this study is undeclared
Woo WK; 2003	Study Type: other Evidence Level: 3	Intervention: None Comparison: None	n=1	Case report of 5 year old boy with long standing severe atopic eczema since 6		At presentation the boy was small for age (height and weight on the 9th centile). Unclear as to whether this was normal for him (mid-parental height 165cm). He was 103 cm.	Adrenal gland suppression should be suspected in any patient who has regularly been using potent TCS and is	This case report is EL=3 as it is an n=1 study

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[522]				months TCS such as betamethasone valerate (0.1%) had been applied continuously at up to 30g per week and clobetasol propionate 0.05% had been applied intermittently over the last year He had asthma from the age of 12 months with moderate severity requiring hospitalisation about twice a year for which he used a beclometasone dipropionate inhaler twice daily		Full biochemical analysis was carried out: Serum IgE 3850 kU/l (range 0-70) Serum cortisol 277 nmol/l (range 300-700) ACTH stimulation showed results at baseline: 8nmol/l (normal >120) 30 mins: 112nmol/l (normal >570) 60 mins: 150nmol/l (normal >570) No steroid skin effects were noted	small for his or her age	
Bode HH 1980 [523]	Study Type: case report Evidence Level: 3	Intervention: None Comparison: None	n=1	A case report of a 13 year old boy who was referred to a paediatric unit due to his short stature. He was born full term with normal birth weight, length and early development. He developed atopic eczema at 18 months which covered most of his body. This was treated with a TCS cream (betamethasone ointment 2%) for 6		At age 13 years Serum cortisol was 0.1ug/dL Plasma ACTH was <10pg/ml Normal thyroid function Bone age was that of a 9 year old boy Therapy was changed to an emulsion ointment base (Eucerin cream) and the use of beclomethasone was limited to wrists and ankles where eczema was still present. 9 days after his first visit, an ACTH stimulation test was performed and the basal ACTH level was unmeasurable, the serum cortisol level was 0.9ug/dL and the latter rose to only		This case report is EL=3 as it is a n=1 study

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				years and this improved his atopic eczema and relieved his discomfort. The quantity of TCS used weekly was 45g. At 13 years, he had a height of 131.7cm (mean for age 155 cm) and he weighed 30kg. His head circumference was 53.3cm, span 128.3cm and upper to lower body segment ratio 0.95. His skin was dry, red, thin and transparent. His face appeared slightly cushingoid and there was hirsutism on both shoulders, arms and forehead.		1.5ug/dL 60 min after ACTH stimulation 7 weeks later (after treatment change) Serum ACTH 57pg/ml Serum cortisol 7.8ug/dL which rose to 22ug/dL after ACTH stimulation. Over the next year, TCS ointment was only used intermittently. In that time the boy grew 7.9cm and showed further advancement of puberty. Bone ages of 11 and 12.5 years were found at 6 and 12 months after change in treatment The eczema was controlled with non-steroidal preparations and the severe pruritus was suppressed with hydroxyzine chloride		
Caffarelli C; [524]	Study Type: Cohort Evidence level: 2-	n=65 children with atopic eczema N=65 children unaffected by atopic eczema	Children (40 boys and 25 girls) with a mean age of 3.55, range 6 months-14 years. Atopic eczema was diagnosed by Hanifin and Rajka criteria. Control children had a mean age 3.65 range 6mths-14 years	Intervention: None Comparison: None	Follow-up period: None Outcome Measures: Questionnaire completed by parents regarding their children's gastrointestinal symptoms including questions on eczema for the affected children's group. Children's skin was examined	Gastrointestinal (GI) symptoms: Diarrhoea (31% vs. 0%, p<0.001), vomiting (18% vs. 3% p<0.01) and regurgitation (38% vs. 17% p<0.001) occurred with greater frequency in the eczema group compared to the controls. Frequency of abdominal pain, distension, eructation and flatulence was also greater in the eczema group compared to controls but not statistically so. In 67% of the eczema children GI symptoms preceded the onset of eczema. No association of severity of eczema and GI symptoms were observed. GI symptoms were more common in children	An increased frequency of GI disorders appears to be associated with the presence of atopic eczema in children and may be critical in some children's failure to thrive.	Interesting data but there may be many confounding factors and the number of children involved is relatively small. The funding of the study is undeclared

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					Weight, height and abdominal circumference Skin prick tests (for affected children's group)	with diffuse (100%) than localised eczema (70%) p<0.05 (95% 0.187 to 0.433) Mean age of onset of GI symptoms Eczema children: 11.2 months (15 days-74 months) Control children : 4.12 months (15 days to 74 months) p<0.05 60% of the children with eczema had at least one positive skin prick test and 54% had a positive skin prick test to one food antigen. whole egg 37% egg yolk 34% egg white 28% whole cows milk 22% etc There was no statistically significant difference in age, height, weight and eleventh-rib circumference between the atopic eczema and control group		
Agostoni C; 2006 [525]	Study Type: Cohort Evidence level: 2-	n=55 children with atopic eczema of which n=36 breastfed and n=19 nonbreastfed n=114 healthy infants of which n=58 breastfed and n=56 nonbreastfed	55 (24 females and 31 males) children born in the maternity unit and subsequently admitted to an allergy clinic at the hospital for symptomatic atopic eczema diagnosed by the Hanifin criteria. The control group were recruited from the maternity unit.	Intervention: None Comparison: None	Follow-up period: None Outcome measures: Body weight and length of atopic eczema children was evaluated retrospectively at diagnosis and then prospectively through the first 12 months of life. The control group were followed up from birth. Measurements were	Atopic eczema and control children were comparable for the baseline characteristics e.g. gestational age, birth weight and length. Mean (SD) age at atopic eczema onset was 3.0 (1.6) months in BF children, 2.4 (1.2) months in non-BF children (p=0.12) Presence of asthma: 13 atopic eczema patients (9BF, 4 non BF) No cases in the control group Patients affected by atopic eczema showed progressive impairment of growth in both WA and LA z scores (p<0.001). Weight	This study showed that in the first year of life, infants with atopic eczema showed a progressive impairment in growth irrespective of the type of early feeding (BF vs non-BF) and that disease severity of the disease may be an independent factor negatively affecting growth.	Despite small numbers it provides interesting data on dietary influences in the first year of life of infants with atopic eczema. The funding of the study is undeclared.

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					made at age 1, 2, 3, 4, 6, 9 and 12 months. Z scores for weight (WA)and length were (LA) calculated from these In addition the following data were recorded: infants birth date mother's age, height, prepregnancy body weight and education level. Familial social status gestational age and parity Severity of atopic eczema (SCORAD), elimination diets and presence of asthma	After onset mean difference -0.27; 95% CI , -0.41 to -0.14 Length After onset mean difference -0.17; 95%CI -0.3 to -0.03 Before the onset of atopic eczema the LA z score was already significantly negative (-0.22; 95% CI:-19 to -0.6) Differences between children with atopic eczema and control children were significant after the second month and more markedly so at 6 months even after adjustment for confounders and type of early feeding (BF vs non-BF). At 12 months the adjusted mean difference was -0.69 (95% CI -1.00 to -0.38) for WA z score and -0.67 (95%CI -0.98 to -0.36 for LA z score In the atopic eczema group an impairment of growth (height and weight) occurred in both the breastfed (p<0.001) and the non-breast fed (p<0.001) infants Analysis to determine any possible association of growth with age of onset, severity of disease, elimination diet or presence of asthma showed that severity of disease was associated with increased WA growth impairment in the second 6 months of life (p<0.05) even after adjusting for confounding factors.		
Isolauri E; [526]	Study Type: Cohort Evidence level: 2-	n=100 children with suspected cow milk allergy n=60 healthy age-matched control children	Children aged 1 to 17 months (mean 7 months) who had been referred to hospital on the basis of suspected cow's milk allergy by a positive open or double-blind, placebo-	Intervention: Cow's milk elimination diet with either an extensively hydrolysed casein or whey formulation (n=44) or a soya formula (n=45) or in older patients with	Follow-up period: 24 months Outcome Measures: Length and weight during the first 24 months of life	The diagnosis of cow's milk allergy was made at 7 months (6-8 months) The reactions involved pruritus, urticaria, morbilliform exanthema or reactions of an eczematous type. The relative length of children decreased	It was concluded that co-ordinated dietetic and paediatric evaluation is needed for evaluation of allergies so as to avoid unnecessary elimination diets and encourage compliance to the individually tailored	The eczematous status of the children is unclear and no details of the eczema are given in the results of the

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
			controlled cow's milk challenge. Their atopic eczema was diagnosed by the Hannifin criteria. Control children were recruited from a well-baby clinic.	a calcium supplement Comparison: None	Length for age and weight for length SDS were calculated	compared to the healthy control group (p<0001). The fall in length coincided with the onset of symptoms of allergy, and the start of the elimination diet. (Patients were divided into two groups) Early onset group (3-6 months)p=0.003 Later onset group (6-10 months)p=0.009 No catch up was seen at 24 months. The relative weight in patients continued to fall compared with that in the control group p=0.03 The delay on growth was more pronounced in a subgroup of patients with early onset than in late onset patients (p<0.0001). Low serum albumin was present in 6% of children 24% had abnormal urea concentration 8%had a low serum phospholipid docosaheaenoic acid The duration of breast feeding correlated positively with the sum of n-3 polyunsaturated fatty acids (p=0.001) and with the relative amount of docosahexaenoic acid (p=0.002)	elimination diets.	study. The funding of this study is undeclared.
Laitinen K; [527]	Study Type: other Evidence level: 3	n=159 children	Children with a family history of atopic eczema (mother, father and/or older sibling) and who had previously participated in a prenatal probiotic study.	Intervention: Supplementation with Lactobacillus rhamnosus Strain GG; ATCC 53 103 was administered to the children postnatally for 6 months Comparison: None	Follow-up period: 48 months Outcome Measures: Children were followed for 4 years with study visits at 3 weeks, and at 3,6,12,18, 24 and 48 months at which the following were measured Weight Height	Atopic eczema was diagnosed in 29% (46/159) at 6 months, 46% (65/140) at 12 months, 35% (46/132) at 24 months and 36% (39/107) at 48 months. Cow's milk allergy was diagnosed in 14% in 18 children at 12 months Logistic regression analysis showed that increased intakes of retinol, calcium and zinc (i.e. taking the probiotic diet) reduced the risk of atopic eczema whilst an increase of ascorbic acid increased the chances of atopic eczema. Probiotic administration was not associated with any detrimental effect on growth overall at 48 months	Administration of a perinatal supplement with probiotics had no detrimental effect on growth but may have some effect on the incidence of atopic eczema. The presence of atopic eczema appeared to have an effect on the growth of children up to the age of 48 months	This is a complex study with detailed analysis. The results are interesting but more evidence is needed before a probiotioc supplement could be advocated. Importantly the supplement appears safe and has no effect

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
					at 48 months Biceps, triceps and suprailiac skinfold thickness mid upper arm thickness SDS scores and weight for height % were calculated using Finnish reference values. Diagnosis of eczema was by Hanifin and cow's milk allergy was diagnosed by a double blind, placebo controlled challenge. Dietary intake was recorded at 6,12 and 48 months with 4 day diaries	Height mean difference 0.04 SDS 95% CI -0.33 to 0.4, p=0.852) Weight for height (mean difference -3.35 (95% CI-7.07,0.37)%, p=0.077) The effect of atopic eczema was significant with respect to weight -5.1 SDS 95%CI -8.9 to -1.2, p=0.001) but not height -0.05 SDS 95% CI -0.42 to 0.33, p=0.815) although mean weight for height in children with atopic eczema was -5.1% 95% CI -8.9-1.2% lower compared with control children (p=0.01) Mid upper arm muscle circumference and proportion of body fat were lower in children with atopic eczema at 48 months (p=0.041 and p=0.007, respectively).		detrimental effect on growth The funding of this study is undeclared.
Estrada-Reyes E; [528]	Study Type: Other Evidence Level: 3	Intervention: Extensively hydrolysed milk formula for 1 year adminstered according to weight and age. Comparison: None	n=45 infants and toddlers	Children 6 (1.0 to 27) months with a positive history of cow's milk allergy confirmed by a positive skin prick test and high IgE levels for either alpha-lactalbumin, beta-lactoglbulin or casein and positive single-blind food challenge	Sex normalised percentiles of heights and weights of infants and toddlers before enrolment and after study (1 year).	Results for all children (atopic eczema and bronchitis) Percentile weights (CI 95% -3.1 to -2.3) and heights (CI 95% -5.2 to 8.1) at baseline were similar to those at 1 year of follow up. Correlation coefficients at baseline and year one: Weight 0.85 (95% CI, 0.74 to 0.92, p<0.001) Height 0.87 (95% CI 0.76 to 0.92, p<0.001) Between weight and height at baseline 0.93 (95% CI , 0.88 to 0.96; p<0.0001) and year one 0.95 (95% 0.92 to0.97; p<0.001) Multivariate analysis showed that sex, breastfeeding, early bottlefeeding, ingestion of adapted or special milk formulas, atopic eczema were not correlated with either the	Growth of infants and toddlers with cow's milk allergy was not affected by the intake of extensively hydrolysed milk for one year. The presence of atopic eczema in this population did not appear to have any deleterious effect on these children's growth.	It was a small study and many other confounding factors e.g. other illness, social class need to be considered. Children with atopic eczema formed aa small (n=13) proportion of the study population and therefore the effect on growth in the atopic eczema

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						children's weight or height at diagnosis of allergy or at 1 year of follow up (p>.10) Atopic eczema was reported in 18 (40%) of patients at the beginning of study and 13 (28.9%) at the end. Weights (95% CI -0.6 to 2.6) and heights (95% CI -1.5 to 9.5) were not different between toddlers who had atopic eczema during the study period and those who did not (p>0.05).		population as a whole is difficult to extrapolate. The funding of this study is undeclared

Indications for referral

No evidence tables.

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