National Collaborating Centre for
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
Funded to produce guidelines for the NHS by NICE

Update information

June 2023: NICE's original guideline on atopic eczema was published in 2007. Section 7.1 has been amended by the 2023 update, which reviewed the evidence on emollient bath additives.

See the NICE website for the guideline recommendations and the evidence review for the 2023 update. This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2023.

Atopic eczema in children

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

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

Commissioned by the National Institute for Health and Clinical Excellence

December 2007

RCOG Press

Published by the **RCOG Press** at the Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG

www.rcog.org.uk

Registered charity no. 213280

First published 2007

ISBN 978-1-904752-42-4

RCOG Editor: Andrew Welsh
Original design: FiSH Books, London
Typesetting: Andrew Welsh
Proofreading: Katharine Timberlake (Reedmace Editing)
Index: Jan Ross (Merrall-Ross (Wales) Ltd)
Printed by Bell & Bain, 303 Burnfield Road, Thornliebank, Glasgow G46 7UQ

Contents

Guideline Development Group membership and acknowledgements

Guideline Development Group

GDG member	Job title and affiliation	Area of expertise
Denise Carr	General Practitioner with Special Interest in Dermatology, Beckenham, Kent	General practitioner
Christine Clark	Medical Writer and Independent Pharmaceutical Consultant	Pharmacist
Michael Cork	Head of Academic Dermatology, Academic Unit of Biomedical Genetics – Dermatology, The University of Sheffield School of Medicine and Biomedical Sciences and Honorary Consultant Dermatologist at Sheffield Children's Hospital and Sheffield Teaching Hospitals NHS Foundation Trust	Dermatologist
Helen Cox	Consultant in Paediatric Allergy and Immunology, Imperial College Healthcare NHS Trust, London	Paediatrician with an interest in allergy
Elizabeth Gilmour	Consultant Dermatologist, Tameside General Hospital and Booth Hall Children's Hospital, Manchester	Dermatologist
Wendy Lancaster	Health Visitor, North Yorkshire and York Primary Care Trust	Health visitor
Sandra Lawton	Nurse Consultant Dermatology, Dermatology Department, Queen's Medical Centre, Nottingham University Hospitals NHS Trust	Dermatology specialist nurse
Sue Lewis-Jones	Consultant Dermatologist, Ninewells Hospital, Dundee and Honorary Senior Lecturer, University of Dundee	Dermatologist (GDG chair)
Sarah Purdy	Consultant Senior Lecturer in Primary Health Care, University of Bristol and General Practitioner, Bristol	General practitioner
Amanda Roberts	General Manager, DAX Products Ltd and Marketing and Development Manager, The Home Improvement Trust	Patient/carer representative
Jean Robinson	Clinical Nurse Specialist, Paediatric Dermatology, Barts and The London NHS Trust	Dermatology specialist nurse
Sue Ward	Information and Education Manager, National Eczema Society	Patient/carer representative
NCC-WCH staff		
Paula Broughton-Palmer	Senior Work Programme Coordinator	Guideline methodologist
Hannah-Rose Douglas	Senior Health Economist	Guideline methodologist
Alyson Huntley	Freelance Systematic Reviewer	Guideline methodologist
Moira Mugglestone	Deputy Director	Guideline methodologist (NCC-WCH project director)
Anne Marie O'Connell	Information Specialist	Guideline methodologist
Julia Saperia	Research Fellow	Guideline methodologist

External advisers

External adviser	Job title and affiliation	Area of expertise
Carolyn Charman	Consultant Dermatologist, Royal Devon and Exeter NHS Foundation Trust	Scoring and measurement of severity of atopic eczema
Stephen Greene	Reader in Child and Adolescent Health, Maternal and Child Health Sciences, University of Dundee, Ninewells Hospital and Medical School, Dundee	Paediatric endocrinologist
C Anthony Hart	Professor and Honorary Consultant in Medical Microbiology, University of Liverpool and Alder Hey Children's Hospital, Liverpool	Medical microbiologist
Penny Titman	Clinical Psychologist, Great Ormond Street Hospital, London	Clinical psychologist
Hywel Williams	Director, Centre of Evidence Based Dermatology, University of Nottingham	Dermato-epidemiologist with an interest in atopic eczema

Acknowledgements

We thank the following NCC-WCH staff who provided additional support: Adebayo Akande, Anna Burt and Beti Evans. We also thank the Patient and Public Involvement Programme (PPIP) of the National Institute for Health and Clinical Excellence (NICE) whose glossary was adapted for use in this guideline. Finally, we pay tribute to Tony Hart, who died during the development of the guideline. In his capacity as external adviser to the GDG, Tony presented a welcome blend of expertise and good humour. We offer our condolences to his family.

Stakeholder organisations

Addenbrooke's NHS Trust
Alliance Pharmaceuticals
Alpro UK Ltd
Association of Child Psychotherapists
Association of the British Pharmaceutical Industry (ABPI)
Astellas Pharma Ltd
Barnsley Hospital NHS Foundation Trust
Barnsley PCT
Barts and the London NHS Trust
Bedfordshire PCT
Breakspear Medical Group Ltd
Brighton and Sussex University Hospitals NHS Trust
British Association for Counselling and Psychotherapy (BACP)
British Association of Dermatologists
British Dermatological Nursing Group
British Dietetic Association
British Homeopathic Association
British National Formulary (BNF)
British Psychological Society
British Society for Allergy & Clinical Immunology (BSACI)
Calderdale PCT
CASPE
Centre of Evidence Based Dermatology
Changing Faces
CIS'ters
Clinovia Ltd
Commission for Social Care Inspection
Community Practitioners and Health Visitors Association
Connecting for Health
Conwy & Denbighshire NHS Trust

Cornwall & Isles of Scilly PCT
Crookes Healthcare Ltd
David Lewis Centre, The
Department of Health
Department of Health, Social Security and Public Safety of Northern Ireland
Derbyshire Mental Health Services NHS Trust
Dermal Laboratories Ltd
Developing Patient Partnerships
Education for Health
Fibroid Network Charity
GlaxoSmithKline UK
Guy's and St Thomas' NHS Trust
Health and Safety Executive
Health Commission Wales
Healthcare Commission
Heart of England NHS Foundation Trust
Hermal
Hertfordshire Partnership NHS Trust
Islington PCT
King's College Hospital NHS Trust
Leeds PCT
LEO Pharma
Liverpool PCT
Luton and Dunstable Hospital NHS Trust
Maidstone and Tunbridge Wells NHS Trust
Medicines and Healthcare products Regulatory Agency (MHRA)
Medicines for Children Research Network (MCRN)
Medihoney (Europe) Ltd
Menarini Diagnostics
Mid Yorkshire NHS Trust
Milton Keynes PCT
Molnlycke Health Care
National Coordinating Centre for Health Technology Assessment (NCCHTA)
National Eczema Society
National Patient Safety Agency
National Pharmacy Association
National Public Health Service – Wales
Neonatal & Paediatric Pharmacists Group (NPPG)
Newcastle PCT
NHS Clinical Knowledge Summaries Service
NHS Health and Social Care Information Centre
NHS Plus
NHS Quality Improvement Scotland
North Eastern Derbyshire PCT
Northwest London Hospitals NHS Trust
Nottingham City PCT
Novartis Pharmaceuticals UK Ltd
Nutricia Ltd
PERIGON (formerly the NHS Modernisation Agency)
Primary Care Dermatology Society
Primary Care Pharmacists Association
PRIMIS+
Prodigy
Reckitt Benckiser Healthcare (UK) Ltd
Regional Public Health Group – London
Royal College of General Practitioners
Royal College of Midwives
Royal College of Nursing
Royal College of Paediatrics and Child Health
Royal College of Physicians of London
Royal College of Psychiatrists

Royal Pharmaceutical Society of Great Britain
Royal Society of Medicine
Sandwell PCT
Schering-Plough Ltd
Scottish Intercollegiate Guidelines Network (SIGN)
Sedgefield PCT
Sheffield Children's Hospital NHS Trust
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Sinclair Pharmaceutical Ltd
Skin Care Campaign
Staffordshire Moorlands PCT
Stiefel Laboratories
Stockport PCT
Tameside and Glossop Acute Services NHS Trust
TIPS Ltd
University College London Hospitals NHS Foundation Trust
University of Hertfordshire
Walsall Teaching PCT
Welsh Assembly Government (formerly National Assembly for Wales)
Welsh Scientific Advisory Committee (WSAC)
West Hertfordshire Hospitals Trust
West Middlesex University Hospital NHS Trust
Western Cheshire PCT
Wiltshire PCT
York NHS Trust

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

Glossary of terms

Allergen An allergen is a complex mixture of proteins capable of eliciting an immediate **hypersensitivity** (allergic) response by inhalation, ingestion or contact with the skin.

Anaphylaxis An acute, severe, life-threatening **systemic hypersensitivity** (allergic) reaction resulting in skin rashes, nausea, vomiting, swelling of the mouth and tongue, wheezing, a sudden drop in blood pressure, collapse and even sudden death.

Antibody A protein produced by blood cells to protect the body against foreign proteins such as infectious diseases. Antibodies that cause allergic responses may sometimes be produced.

Antigen Any substance that may be specifically bound by any antibody molecule.

Appraisal of evidence Formal assessment of the quality of research evidence and its relevance to the clinical question or guideline under consideration, according to predetermined criteria.

Atopic dermatitis See **atopic eczema**.

Atopic eczema A chronic inflammatory skin condition characterised by an itchy red rash that favours the skin creases such as folds of elbows or behind the knees. The word 'atopic' in the term atopic eczema is an indicator of the frequent association with atopy and the need to separate this clinical phenotype from the ten or so other forms of eczema such as irritant, allergic contact, discoid, venous, seborrhoeic and photosensitive eczema. The terms **atopic eczema** and **atopic dermatitis** are synonymous.

Atopic sensitisation A genetic predisposition to become sensitised and produce **IgE** antibodies in response to allergens commonly occurring in the environment. Elevated levels of specific IgE antibody to food or environmental allergens may be detected in these individuals.

Atopy A personal or family tendency to become sensitised and produce IgE antibodies. As a consequence these, people can develop symptoms of eczema, asthma and/or hay fever (allergic or perennial rhinitis or rhinoconjunctivitis).

Atopy patch test (APT) A test in which whole food or inhaled allergen proteins are applied to the skin under occlusion for 24 hours. The test site is evaluated at the time of removal and 2 days later for evidence of inflammation that can be scored by severity. Controls are applied to determine possible **irritant** reactions.

Bias Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually does not. Bias can occur by chance or as a result of **systematic errors** in the design and execution of a study. Bias can occur at different stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data. For examples see **selection bias**, **performance bias**, **information bias**, **confounding**, **publication bias**.

Blinding or masking The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a **placebo** (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against **bias**. See also **double-blind study**, **single-blind study**.

Body mass index (BMI) A person's weight (in kilograms) divided by the square of their height (in metres). It is used as a measure of underweight, overweight or obesity.

Case–control study A study that starts with the identification of a group of individuals sharing the same characteristics (e.g. people with a particular disease) and a suitable comparison (**control**) group (e.g. people without the disease). All subjects are then assessed with respect to things that happened to them in the past, e.g. things that might be related to getting the disease under investigation. Such studies are also called **retrospective** as they look back in time from the outcome to the possible causes.

Case report (or case study) Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.

Case series Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (**control**) group of patients.

Causal relationship Describes the relationship between two **variables** whenever it can be established that one causes the other. For example, there is a causal relationship between a treatment and a disease if it can be shown that the treatment changes the course or outcome of the disease. Usually **randomised controlled trials** are needed to ascertain causality. Proving cause and effect is much more difficult than just showing an association between two variables. For example, if it happened that everyone who had eaten a particular food became sick, and everyone who avoided that food remained well, then the food would clearly be associated with the sickness. However, even if leftovers were found to be contaminated, it could not be proved that the food caused the sickness unless all other possible causes (e.g. environmental factors) had been ruled out.

Childhood Atopic Dermatitis Impact Scale (CADIS) A hypothesis-based quality of life survey to measure the impact of atopic eczema on children aged up to 8 years and their families. It covers four domains (physical health, emotional health, physical functioning, and social functioning). It is a 45-item scale using a five-category choice method (score 0–180).

Childhood Psychopathology Measurement Schedule (CPMS) The questionnaire consists of 51 statements and includes assessment of intelligence with behaviour, conduct, anxiety and depression disorders. The answer is scored 0 if often not true and 1 if often true and thus the higher the score, the higher the psychopathology.

Children's Dermatology Life Quality Index (CDLQI) A condition-specific measure of the quality of life impact of any skin disease on children aged 4–16 years. It comprises a ten-question scale in written or cartoon form which assesses the domains of physical, social and psychological impact (symptoms and emotions, social relationships, schooling, recreation, sleep and treatment difficulties) of atopic eczema over the previous week. Each question has four answers: not at all = 0, a little = 1, a lot = 2, very much = 3. Thus 0 is the best score and 3 the worst score. The maximum score is 30. It is available in over 20 languages.

Children's Illness Perception Questionnaire (CIPQ) A 26-item self-report instrument consisting of two sections. One section concerns children's illness beliefs regarding the timeline, consequences and control/cure of their illness and the other section children's beliefs regarding the causes of their condition. Responses are rated in a dichotomous manner as true or false.

Children's Life Quality Index (CLQI) A generic health-related, quality of life proxy measure of 12 simple questions relating to the previous 3 months, investigating physical, social and psychological impact of a child's health problem. It is scored in a similar way to the CDLQI

Clinical audit A **systematic** process for setting and monitoring standards of clinical care. Whereas 'guidelines' define what the best clinical practice should be, 'audit' investigates whether best practice is being carried out. Clinical audit can be described as a cycle or spiral. Within the cycle there are stages that follow a systematic process of establishing best practice, measuring care against specific criteria, taking action to improve care, and monitoring to sustain improvement. The spiral suggests that as the process continues, each cycle aspires to a higher level of quality.

Clinical effectiveness The extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical 'effectiveness' is not the same as **efficacy**.

Clinical question This term is sometimes used in guideline development work to refer to the questions about treatment and care that are formulated in order to guide the search for research evidence. When a clinical question is formulated in a precise way, it is called a **focused question**.

Clinical trial A research study conducted with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses controlled clinical trials and **randomised controlled trials**.

Clinician A qualified healthcare professional providing patient care, e.g. doctor, nurse, physiotherapist.

Cluster A group of patients, rather than an individual, used as the basic unit for investigation. See also **cluster design**, **cluster randomisation**.

Cluster design Cluster designs are those where research subjects are not sampled or selected independently, but in a group. For example a clinical trial where patients in a general practice are allocated to the same intervention; the general practice forming a cluster. See also **cluster**, **cluster randomisation**.

Cluster randomisation A study in which groups of individuals (e.g. patients in a GP surgery or on a hospital ward) are randomly allocated to treatment groups. Take, for example, a smoking cessation study of two different interventions – leaflets and teaching sessions. Each GP surgery within the study would be randomly allocated to administer one of the two interventions. See also **cluster**, **cluster design**.

Cochrane Collaboration An international organisation in which people find, appraise and review specific types of studies called **randomised controlled trials**. The Cochrane Database of Systematic Reviews contains regularly updated reviews on a variety of health issues and is available electronically as part of the **Cochrane Library**.

Cochrane Library The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of **randomised controlled trials** prepared by the **Cochrane Collaboration**). The Cochrane Library is available on CD-ROM and the Internet.

Cohort A group of people sharing some common characteristic (e.g. patients with the same disease), followed up in a research study for a specified period of time.

Cohort study An **observational study** that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, e.g. comparing mortality between one group that received a specific treatment and one group which did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or '**prospective**' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or '**retrospective**' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.

Confidence interval (CI) A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.

Confounder or confounding factor Something that influences a study and can contribute to misleading findings if it is not understood or appropriately dealt with. For example, if a group of people exercising regularly and a group of people who do not exercise have an important age difference then any difference found in outcomes about heart disease could well be due to one group being older than the other rather than due to the exercising. Age is the confounding factor here and the effect of exercising on heart disease cannot be assessed without adjusting for age differences in some way.

Consensus methods A variety of techniques that aim to reach an agreement on a particular issue. Formal consensus methods include **Delphi** and **nominal group** techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic.

Consensus statement A statement of the advised course of action in relation to a particular clinical topic, based on the collective views of a body of experts.

Consistency The extent to which the conclusions of a collection of studies used to support a guideline recommendation are in agreement with each other. See also **homogeneity**.

Control group A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) – in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.

Cost-effectiveness Value for money. A specific healthcare treatment is said to be 'cost-effective' if it gives a greater health gain than could be achieved by using the resources in other ways.

Cost-effectiveness analysis	A type of **economic evaluation** comparing the costs and the effects on health of different treatments. Health effects are measured in 'health-related units', for example, the cost of preventing one additional heart attack.
Cost–utility analysis	A special form of **cost-effectiveness analysis** where health effects are measured in **quality-adjusted life years (QALYs)**. A treatment is assessed in terms of its ability to both extend life and to improve the quality of life.
Crossover study design	A study comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A, B and half to receive them in the order B, A. A problem with this study design is that the effects of the first treatment may carry over into the period when the second is given. Therefore a crossover study should include an adequate 'wash-out' period, which means allowing sufficient time between stopping one treatment and starting another so that the first treatment has time to wash out of the patient's system.
Cross-sectional study	The observation of a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a **longitudinal study** which follows a set of people over a period of time.)
Cytokine	A small protein released by cells that has a specific effect on the interactions between cells, on communications between cells or on the behaviour of cells. The cytokines include the interleukins, lymphokines and cell signal molecules, such as tumour necrosis factor and the interferons, which trigger inflammation and respond to infections.
Declaration of interest	A process by which members of a working group or committee 'declare' any personal or professional involvement with a company (or related to a technology) that might affect their objectivity, e.g. if their position or department is funded by a pharmaceutical company.
Delphi technique	A technique used for the purpose of reaching an agreement on a particular issue, without the participants meeting or interacting directly. It involves sending participants a series of postal questionnaires asking them to record their views. After the first questionnaire, participants are asked to give further views in the light of the group feedback. The judgements of the participants are statistically aggregated, sometimes after weighting for expertise. See also **consensus methods**.
Dermatitis Family Impact (DFI) scale	A condition-specific scale that measures the impact of childhood atopic eczema on family life over the previous week and is based on ten items: housework, food preparation, sleep of other family members, leisure activities such as swimming, time spent on shopping, costs related to treatment or clothes, tiredness or exhaustion, emotional distress, relationships in the family and the impact of helping with treatment on the life of the main carer. It is a one-page questionnaire. Scoring is similar to that of the CDLQI.
Diagnostic study	A study to assess the effectiveness of a test or measurement in terms of its ability to accurately detect or exclude a specific disease.
Double-blind placebo-controlled food challenge (DBPCFC)	The gold standard test for diagnosing food allergy. The patient receives two food challenge tests, one with the active ingredient (food allergen) and one without (placebo). The procedure is double blind when both patient and investigator are unaware of which food contains the active ingredient. See also **open food challenge**.
Double-blind study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment or intervention the subject is receiving. The purpose of **blinding** is to protect against **bias**.
Economic evaluation	A comparison of alternative courses of action in terms of both their costs and consequences. In **health economic** evaluations the consequences should include health outcomes.
Effectiveness	See **clinical effectiveness**.
Efficacy	The extent to which a specific treatment or intervention, under *ideally controlled conditions* (e.g. in a laboratory), has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care.
Elective	Name for clinical procedures that are regarded as advantageous to the patient but not urgent.
Elimination diet	Elimination of a food from a patient's diet to determine whether the patient's symptoms resolve when foods are excluded from the diet.
Emollient	An agent that acts as a moisturiser to soothe and soften the skin.
Empirical	Based directly on experience (observation or experiment) rather than on reasoning alone.

Epidemiology	Study of diseases within a population, covering the causes and means of prevention.
Erythema	Redness.
Evidence based	The process of systematically finding, appraising and using research findings as the basis for clinical decisions.
Evidence level (EL)	A code (e.g. 1++, 1+) linked to an individual study, indicating where it fits into the **hierarchy of evidence** and how well it has adhered to recognised research principles.
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Excoriation	Scratch mark.
Experimental study	A research study designed to test whether a treatment or intervention has an effect on the course or outcome of a condition or disease – where the conditions of testing are to some extent under the control of the investigator. **Randomised controlled trial** is an example of an experimental studys.
External validity	The degree to which the results of a study hold true in non-study situations, e.g. in routine clinical practice. May also be referred to as the **generalisability** of study results to non-study patients or populations.
Extrapolation	The application of research evidence based on studies of a specific population to another population with similar characteristics.
Exudation	Oozing of fluid (serum) onto the surface of the skin, which occurs when the superficial layer of skin has been damaged or removed, usually through scratching. Dries to leave crusts.
Flexural	Relating to a bend in a body part or organ.
Focused question	A study question that clearly identifies all aspects of the topic that are to be considered while seeking an answer. Questions are normally expected to identify the patients or population involved, the treatment or intervention to be investigated, what outcomes are to be considered, and any comparisons that are to be made. For example, do insulin pumps (intervention) improve blood sugar control (outcome) in adolescents with type 1 diabetes (population) compared with multiple insulin injections (comparison)? See also **clinical question**.
Food allergy	A hypersensitivity reaction initiated by specific immunological mechanisms in response to a specific food allergen. An adverse immune response to food proteins.
Funnel plot	Funnel plots are simple scatter plots on a graph. They show the treatment effects estimated from separate studies on the horizontal axis against a measure of sample size on the vertical axis. **Publication bias** may lead to asymmetry in funnel plots.
General Health Questionnaire (GHQ)	A questionnaire for screening for mental health difficulties in adults. The 28-item version uses a binary score system with a cut-off point of 5. Examples of questions include: • Have you felt that you are ill? • Have you lost sleep over worry?
Generalisability	The extent to which the results of a study hold true for a population of patients beyond those who participated in the research. See also **external validity**.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in bibliographic retrieval systems.
Guideline	A systematically developed tool that describes aspects of a patient's condition and the care to be given. A good guideline makes recommendations about treatment and care based on the best research available, rather than opinion. It is used to assist clinician and patient decision making about appropriate health care for specific clinical conditions.
Guideline recommendation	Course of action advised by the guideline development group on the basis of their assessment of the supporting evidence.
Health economics	A branch of economics that studies decisions about the use and distribution of healthcare resources.
Health technology	Health technologies include medicines, medical devices such as artificial hip joints, diagnostic techniques, surgical procedures, health promotion activities (e.g. the role of diet versus medicines in disease management) and other therapeutic interventions.

Height velocity The rate of growth. It can be calculated and compared with the normal growth rate of children the same age using centile charts. Measuring height velocity involves recording a child's height at two time points at least 150 days apart.

Heterogeneity Or lack of **homogeneity**. The term is used in **meta-analyses** and **systematic reviews** when the results or estimates of effects of treatment from separate studies seem to be very different in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of **variables** or duration of follow-up.

Hierarchy of evidence An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions that can be drawn from a well-conducted study. Well-conducted **randomised controlled trials** (RCTs) are at the top of this hierarchy. (Several large statistically significant RCTs which are in agreement represent stronger evidence than say one small RCT.) Well-conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence.

Homogeneity This means that the results of studies included in a **systematic review** or **meta-analysis** are similar and there is no evidence of **heterogeneity**. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also **consistency**.

Hospital Anxiety and Depression Scale (HADS) This is a widely used self-report questionnaire for screening for anxiety and depression among people with physical health problems and is not specific to atopic eczema. It consists of 14 questions, half assessing feelings of anxiety and half feelings of depression. Each question can be answered on a 0–3 scale with total scores of 0–7 being normal, 8–10 being borderline and 11–21 being abnormal.

Hypersensitivity Abnormal responsiveness to the presence of a particular antigen which may cause a variety of allergic reactions.

Immunocap, Pharmacia CAP system FEIA or Unicap A serum 'fluorescent immunoassay' which gives an automated quantitative assay of food-specific IgE levels. A modification of the **radioallergosorbent test (RAST)**.

Immunoglobulin E (IgE) and Immunoglobulin G (IgG) Part of a group of structurally related proteins (gamma-globulins) that act as antibodies. Several classes of Ig with different functions are distinguished – IgA, IgD, IgE, IgG and IgM. High levels of IgE are seen in many people with atopic diseases and play a part in producing allergic reactions to foods and inhalant allergens. Sometimes IgG antibodies may act in a similar fashion.

Impetiginisation Infection of the skin with bacterial organisms, particularly *Staphylococcus aureus* but sometimes streptococcal species. Causes yellowish crusts, pustules and fragile superficial blisters.

Inclusion criteria See **selection criteria**.

Infants' Dermatitis Quality of Life (IDQoL) index A condition-specific proxy measure of the quality of life impact of atopic eczema in infants and children aged 0–4 years. It comprises a one-page questionnaire with ten questions pertaining to the previous week, derived from parental information about the impact of atopic eczema plus an additional question on parent's perception of global severity. It is similar in format and scoring to the CDLQI. The maximum score is 30, and the greater the score the greater the impact on quality of life. It is available in 15 languages.

Information bias Pertinent to all types of study and can be caused by inadequate questionnaires (e.g. difficult or biased questions), observer or interviewer errors (e.g. lack of **blinding**), response errors (e.g. lack of blinding if patients are aware of the treatment they receive) and measurement error (e.g. a faulty machine).

Intention-to-treat analysis An analysis of a clinical trial where patients are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they had dropped out, fully complied with the treatment, or crossed over and received the alternative treatment. Intention-to-treat analyses are favoured in assessments of clinical effectiveness as they mirror the non-compliance and treatment changes that are likely to occur when the treatment is used in practice.

Internal validity Refers to the integrity of the study design.

Intervention Healthcare action intended to benefit the patient, e.g. drug treatment, surgical procedure, psychological therapy, etc.

Irritant Any material that causes irritation of a tissue. An irritant reaction is not caused by an immune response in contrast to an allergic response.

Kappa score or rating A measure of agreement between two individuals or variables, where 1 indicates perfect agreement.

Level of evidence	See **evidence level**.
Lichenification	Exaggeration of the skin markings associated with skin thickening caused by chronic scratching and/or rubbing.
Longitudinal study	A study of the same group of people at more than one point in time. (This type of study contrasts with a **cross-sectional study**, which observes a defined set of people at a single point in time.)
Meta-analysis	Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible, e.g. because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also **systematic review** and **heterogeneity**.
Methodological quality	The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.
Methodology	The overall approach of a research project, e.g. the study will be a **randomised controlled trial**, of 200 people, over one year.
Microbial resistance	The ability of microorganisms to withstand an antibiotic to which they were once sensitive.
Microbial sensitivity	Microbial susceptibility (stalling or killing) of microorganisms to antibiotics.
Multicentre study	A study where subjects were selected from different locations or populations, e.g. a co-operative study between different hospitals; an international collaboration involving patients from more than one country.
Negative predictive value (NPV)	The proportion of people with a negative test result who do not have the disease (where not having the disease is indicated by the **gold standard** test being negative).
Nominal group technique	A technique used for the purpose of reaching an agreement on a particular issue. It uses a variety of postal and direct contact techniques, with individual judgements being aggregated statistically to derive the group judgement. See also **consensus methods**.
Objective measure	A measurement that follows a standardised procedure that is less open to subjective interpretation by potentially biased observers and study participants.
Observation	Observation is a research technique used to help understand complex situations. It involves watching, listening to and recording behaviours, actions, activities and interactions. The settings are usually natural, but they can be laboratory settings, as in psychological research.
Observational study	In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (e.g. whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. There is a greater risk of **selection bias** than in **experimental studies**.
Occlusion	In the context of this guideline, occlusion refers to the application of a specific covering of the skin, such as a bandage or medicated dressing.
Odds ratio (OR)	Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a **confidence interval**) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the **relative risk** (which uses actual risks and not odds) will be very similar. See also **relative risk** and **risk ratio**.
Oedema	Swelling of the skin due to collection of tissue fluids.
Oozing	See **exudation**.
Open food challenge	The administration of food(s) to screen for an allergic reaction in the clinical setting.
Outcome	The end result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

***P* value**	If a study is done to compare two treatments then the *P* value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the *P* value was $P = 0.03$. What this means is that if there really was no difference between treatments then there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of *P* is below 0.05 (i.e. less than 5%) the result is seen as statistically significant. Where the value of *P* is 0.001 or less, the result is seen as highly significant. *P* values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the **confidence interval**.
Papulation	Development of small raised firm lesions (usually less than 5 mm).
Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD)	A dermatology-specific scale to assess the quality of life of parents of children with atopic eczema. It adopted the needs-based model of quality of life which postulates that life gains its quality from the ability and capacity of individuals to fulfil their needs. According to this model, functions such as physical activities, hobbies and socialising are important only insofar as they provide the means by which needs are fulfilled. It consists of 28 items with a dichotomous response format (i.e. score 0–28).
PQoL-AD: Quality of Life in Parents of Children with Atopic Dermatitis	A 26-item scale that addresses five quality of life themes in parents of children with atopic eczema: psychosomatic wellbeing, effects on social life, confidence in medical treatment, emotional coping and acceptance of the disease. Each item requires a response on the scale 1–5.
Peer review	Review of a study, service or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional and/or patient/carer representatives.
Performance bias	Systematic differences in care provided apart from the intervention being evaluated. For example, if study participants know they are in the **control group** they may be more likely to use other forms of care; people who know they are in the experimental group may experience placebo effects, and care providers may treat patients differently according to what group they are in. Masking (**blinding**) of both the recipients and providers of care is used to protect against performance bias.
Personality Trait Inventory (PTI)	A self-report questionnaire that investigates nine areas of maternal personality and mental distress. This standard, validated questionnaire consists of 90 questions exploring activity, cyclothymia, superego, dominance, paranoid tendency, depressive tendency, emotional instability, introversion and social desirability. The score is 0 if the trait is absent, 1 if a positive trait is present and 2 if a negative trait is present.
Piers–Harris Children's Self-Concept Scale	A 60–80 item self-report instrument used to assess self-concept in children and adolescents and consisting of six cluster scales of behaviour, intellectual and school status, physical appearance and attributes, anxiety, popularity, and happiness and satisfaction.
Pilot study	A small-scale 'test' of the research instrument. For example, testing out (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full-scale study begins.
Placebo	Placebos are fake or inactive treatments received by participants allocated to the **control group** in a clinical trial that are indistinguishable from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any placebo effect due to receiving care or attention.
Positive predictive value (PPV)	The proportion of people with a positive test result who have the disease (where having the disease is indicated by the **gold standard** test being positive).
Primary care	Health care delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.
Probability	How likely an event is to occur, e.g. how likely a treatment or intervention will alleviate a symptom.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are **retrospective**.

Protocol	A plan or set of steps which defines appropriate action. A research protocol sets out, in advance of carrying out the study, what question is to be answered and how information will be collected and analysed. Guideline implementation protocols set out how guideline recommendations will be used in practice by the NHS, both at national and local levels.
Pruritus	Itching.
Psychosocial	Relating to social interactions between an individual and other people.
Publication bias	Studies with statistically significant results are more likely to get published than those with non-significant results. **Meta-analyses** that are exclusively based on published literature may therefore produce biased results.
PUVA	PUVA is a type of photochemotherapy. It combines psoralen, a light-sensitive drug, with exposure to ultraviolet A light.
Qualitative research	Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, e.g. a patient's description of their pain rather than a measure of pain. In health care, qualitative techniques have been commonly used in research documenting the experience of chronic illness and in studies about the functioning of organisations. Qualitative research techniques such as focus groups and in-depth interviews have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.
Quality-adjusted life years (QALYs)	A measure of health outcome that looks at both length of life and quality of life. QALYS are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a zero to one scale). One QALY is equal to one year of life in perfect health, or two years at 50% health, and so on.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.
Radioallergosorbent test (RAST)	A serum test to determine antigen-specific IgE antibodies. Similar to CAP test.
Random allocation or Randomisation	A method that uses the play of chance to assign participants to comparison groups in a research study, for example by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of cluster randomisation) being entered into a study has the same chance of receiving each of the possible interventions.
Randomised controlled trial (RCT)	A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or **control group**) receiving an alternative treatment, a **placebo** (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)
Relative body weight	Percentage mean weight for height.
Relative risk (RR)	A summary measure that represents the ratio of the risk of a given event or outcome (e.g. an adverse reaction to the drug being tested) in one group of subjects compared with another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for **risk ratio**.
Reliability	Reliability refers to a method of measurement that consistently gives the same results. For example, someone who has a high score on one occasion tends to have a high score if measured on another occasion very soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession, and if their assessments tend to agree then the method of assessment is said to be reliable.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are **prospective**.
Review	A summary of the main points and trends in the research literature on a specified topic. A review is considered non-systematic unless an extensive literature search has been carried out to ensure that all aspects of the topic are covered and an objective appraisal made of the quality of the studies.

Risk ratio	The ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (**control**) group. The term **relative risk** is sometimes used as a synonym of risk ratio.
Royal Colleges	In the UK medical/nursing world, the term Royal Colleges, as for example in 'The Royal College of …', refers to organisations which usually combine an educational standards and examination role with the promotion of professional standards.
Rutter A2 scale	A parent report questionnaire designed to detect children with a clinically significant degree of psychological disturbances. It consists of 31 statements with a choice of responses, e.g. does the child have temper tantrums, stammers or stutters. Children with an overall score of 13 or more are considered to have a psychological disorder.
Sample	A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.
Scaling	Flakes of outer skin layer appearing as dry skin.
Scottish Intercollegiate Guidelines Network (SIGN)	SIGN was established in 1993 to sponsor and support the development of evidence-based clinical guidelines for the NHS in Scotland.
Secondary care	Care provided in hospitals.
Selection bias	Selection bias has occurred if: • the characteristics of the sample differ from those of the wider population from which the sample has been drawn, or • there are systematic differences between comparison groups of patients in a study in terms of prognosis or responsiveness to treatment.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitisation	Development of antibodies in response to exposure to foreign proteins such as food or inhaled **allergens** which may give rise to an allergic response.
Sensitivity	In diagnostic testing, sensitivity is the proportion of true positive results that are correctly identified as positive by the test. 100% sensitivity means that all those with a negative test result do not have the disease. **Specificity** should be considered alongside sensitivity to fully judge the accuracy of a test.
Single-blind study	A study in which either the subject (patient/participant) or the observer (clinician/investigator) is not aware of which treatment or intervention the subject is receiving.
Skin prick test (SPT)	A skin prick (or puncture) test with foods used to detect a skin response to the material applied to the skin within a short period of time (usually 15–20 minutes). The presence of antigen-specific IgE produces a wheal and flare response.
Skinfold test	A measurement of skinfold thickness taken with the subject standing erect with arms hanging by the side. Measurements can be taken from the triceps (midpoint of upper arm), scapula (inferior angle) and the iliac crest (top of hip bone in mid-axillary line).
Specific indication	When a drug or a device has a specific remit to treat a specific condition and is not licensed for use in treating other conditions or diseases.
Specificity	In diagnostic testing, specificity is the proportion of true negative results that are correctly identified as negative by the test. 100% specificity means that all those with a positive test result have the disease. **Sensitivity** should be considered alongside specificity to fully judge the accuracy of a test.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Standard deviation score (SDS)	SDS or z score is calculated by measuring a particular parameter (or score, e.g. height), subtracting the mean score for people of the same age and dividing the result by the SD for the score at that age using standard measures, e.g. Tanner, Whitehouse and Takaishi standards.
Structured interview	A research technique where the interviewer controls the interview by adhering strictly to a questionnaire or interview schedule with pre-set questions.
Study population	People who have been identified as the subjects of a study.
Study quality	See **methodological quality**.
Study type	The kind of design used for a study. **Randomised controlled trials**, **case–control studies**, and **cohort studies** are all examples of study types.

Subject	A person who takes part in an experiment or research study.
Superinfection	An infection that arises during the course of another infection and is caused by a different microorganism.
Survey	A study in which information is systematically collected from people (usually from a sample within a defined population).
Symptom Questionnaire (SQ)	The SQ can be used to screen for mental health difficulties in adults. The 92-item self-rating scale yields four scales of distress (anxiety, depression, somatisation and hostility-irritability) and four scales of wellbeing (relaxation, contentment, physical wellbeing and friendliness). Scores in the distress scale are in the range 0–17, and in wellbeing scale in the range 0–6.
Systematic	Methodical, according to plan; not random.
Systematic error	Refers to the various errors or biases inherent in a study. See also **bias**.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a **meta-analysis**.
Systemic	Involving the whole body.
Technology appraisal (TA)	A technology appraisal, as undertaken by NICE, is the process of determining the clinical and cost-effectiveness of a **health technology**. NICE technology appraisals are designed to provide patients, health professionals and managers with an authoritative source of advice on new and existing health technologies.
Trust	A trust is an NHS organisation responsible for providing a group of healthcare services. An acute trust provides hospital services. A mental health trust provides most mental health services. A primary care trust buys hospital care on behalf of the local population, as well as being responsible for the provision of community health services.
TW2 method	A method to assess skeletal maturity (bone age) using an X-ray of the fingers, hand and wrist. The bones in the X-ray are compared with the bones of a standard atlas. (TW2RUS is a modified method).
Urticaria	Itchy, red, raised skin wheals of short-lived duration (less than 24 hours), often ring shaped.
Validity	Assessment of how well a tool or instrument measures what it is intended to measure. See also **external validity** and **internal validity**.
Variable	A measurement that can vary within a study, e.g. the age of participants. Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature which can be assessed or measured.
Vehicle	Substance that acts as the medium in which a drug is administered
Weeping	Oozing or exudation.
Z scores	See **standard deviation score**.

1 Introduction

1.1 Atopic eczema

Atopic eczema (atopic dermatitis) is a chronic inflammatory itchy skin condition that develops in early childhood in the majority of cases. It is typically an episodic disease of exacerbation (flares, which may occur as frequently as two or three per month) and remissions, except for severe cases where it may be continuous.[1] Certain patterns of atopic eczema are recognised. In infants, atopic eczema usually involves the face and extensor surfaces of the limbs and, while it may involve the trunk, the napkin area is usually spared. A few infants may exhibit a discoid pattern (circular patches). In older children flexural involvement predominates, as in adults.[2] Diagnostic criteria are discussed in Chapter 3. As with other atopic conditions, such as asthma and allergic rhinitis (hay fever), atopic eczema often has a genetic component. In atopic eczema, inherited factors affect the development of the skin barrier, which can lead to exacerbation of the disease by a large number of trigger factors, including irritants and allergens. Many cases of atopic eczema clear or improve during childhood while others persist into adulthood, and some children who have atopic eczema `will go on to develop asthma and/or allergic rhinitis; this sequence of events is sometimes referred to as the 'atopic march'. The epidemiology of atopic eczema is considered in Chapter 5, and the impact of the condition on children and their families/caregivers is considered in Sections 4.2 and 4.3.

Costs of atopic eczema and implications for the NHS

Two studies conducted in the UK have attempted to calculate the cost burden of atopic eczema in children both to the health service and to the families of children with the condition.

A Scottish study published in 1996 assessed the costs to a semi-rural community in Scotland derived from a year-long study of 146 individuals, 77 of whom were aged under 16 years.[3] The authors reported a mean personal cost of £26 per year (year of prices not given); the maximum spend was £547 per year, of which 81% was due to income loss rather than expenditure. Of those under 16 years, 45% reported no personal cost associated with having atopic eczema. Personal cost per year in the 2–15 year age group was significantly lower than those aged 16 years or over (medians £0.50 and £6.73, $P < 0.05$) and was significantly lower in those aged under 2 years than in those aged 2 years or over (median £0.00, $P < 0.05$). Expenditure across the whole cohort was made up of hospital consultations (8%), over-the-counter treatments (21%), clothing and laundry costs (45%), visits to complementary therapists (4%) and prescriptions in people 16 years or over (7%). A cost was also allocated to loss of income from lost working days due to illness or caring for an ill child (15%).

The mean annual cost to the health service was estimated to be around £16, with the maximum attributable to one patient being £177 (with only two patients costing more than £100 per year). Healthcare costs were associated with use of emollients and bath additives (38%), topical corticosteroids (32%) and bandages (10%), with the remaining 20% being spent on antihistamines, shampoos, antibiotics and evening primrose oil. General practitioner (GP) consultations comprised almost 30% of costs, while hospital consultations made up only 6% of costs. In a separate analysis of severely affected children requiring hospital treatment, the mean hospital cost was £415, and the mean personal costs were £325.

Another UK study of children aged 1–5 years reported mean annual disease costs of £80 per child (1996 prices) with National Health Service (NHS) consultations making up around £29 of those costs and £22 being the costs of prescriptions.[4] The cost to the NHS included GP consultations (50%), health visitors (11%) and practice nurses (4%). Secondary care consultations including accident and emergency (A&E) visits were low (6% of total costs). Prescribing costs comprised 28% of all the NHS costs (around £22 per child). The mean cost to families was estimated to be

£29 and this included the annual cost of purchasing of bedding, clothing, carpets and changes to the home environment. It also included £4 per child for lost income which was experienced by 5% of carers.

International studies of the cost burden of atopic eczema show a pattern of wide variability in costs and a strong positive correlation with the severity of disease.[5-9]

1.2 Aim of the guideline

Clinical guidelines have been defined as 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'.[10] This clinical guideline concerns the management of atopic eczema in children from birth up to the age of 12 years.

It has been developed with the aim of providing guidance on:

- diagnosis and assessment of the impact of the condition
- management during and between flares
- information and education to children and their families/caregivers about the condition.

1.3 Areas outside the remit of the guideline

This guideline does not address:

- primary prevention of atopic eczema or the training of healthcare professionals
- children with infantile seborrhoeic eczema, juvenile plantar dermatosis, primary irritant and allergic contact dermatitis, napkin dermatitis, pompholyx, and photosensitive eczema, except when these conditions occur in association with atopic eczema.

1.4 For whom is the guideline intended?

This guideline is of relevance to those who work in or use the NHS in England, Wales and Northern Ireland, in particular:

- all healthcare professionals who are involved in the care of children who have atopic eczema (including GPs, nurses, pharmacists, dermatologists and paediatricians); the healthcare professionals providing care for children with atopic eczema may vary depending on geographical service provision
- those responsible for commissioning and planning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners, and public health, trust and care home managers
- children with atopic eczema, their families and other caregivers.

A version of this guideline for the public is available from the National Institute for Health and Clinical Excellence (NICE) website (www.nice.org.uk/CG057PublicInfoEnglish) or from the NHS Response Line (0870 1555 455); quote reference number N1428).

1.5 Who has developed the guideline?

The National Collaborating Centre for Women's and Children's Health (NCC-WCH) was commissioned by NICE to establish a multi-professional and lay working group, the Guideline Development Group (GDG), to develop the guideline. The membership of the GDG was determined by the NCC-WCH and NICE, and included the following:

- three dermatologists
- two dermatology specialist nurses
- two GPs
- a health visitor
- a pharmacist
- a paediatrician
- two patient/carer representatives.

Staff from the NCC-WCH provided methodological support for the guideline development process by undertaking systematic searches, retrieving and appraising the evidence, health economic modelling and writing successive drafts of the guideline.

During the development of the guideline the GDG identified a need for expert advice in relation to the assessment of severity of atopic eczema, psychological and psychosocial effects, epidemiology, infections occurring secondarily to atopic eczema, and paediatric growth measurement. Expert advisers were appointed by the GDG to advise on each of these issues, although they were not involved in the final decisions regarding formulation of recommendations.

All GDG members' and external advisers' potential and actual conflicts of interest were recorded on declaration forms provided by NICE and are presented in Appendix A. The forms covered personal pecuniary interests (including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry), personal non-pecuniary interests (including research interests), personal family interests (including shareholdings), and non-personal pecuniary interests (including funding from the healthcare industry for research projects and meetings). The GDG chair and NCC-WCH project director considered all the declarations and concluded that the only one which might be perceived as constituting a material conflict of interest was the GDG chair's personal non-pecuniary interest in the development of quality of life tools. The GDG chair asked other GDG members to chair all discussions regarding evaluation of quality of life tools, and she took no part in recommending her own quality of life tools. The other interests that were declared were not viewed as presenting conflicts of interest because the GDG did not consider recommending any particular products over others (except to take account of licensing restrictions related to the child's age).

Organisations with interests in the management of atopic eczema in children were encouraged to register as stakeholders for the guideline, and registered stakeholders were consulted throughout the guideline development process. The process of stakeholder registration was managed by NICE. The various types of organisation that were eligible to register as stakeholders included:

- national patient and carer organisations that directly or indirectly represent the interests of children with atopic eczema and/or their families/caregivers
- national organisations that represent the healthcare professionals who provide the services for children with atopic eczema and their families/carers
- companies that manufacture the preparations or products used in the management of atopic eczema
- providers and commissioners of health services in England, Wales and Northern Ireland
- statutory organisations such as the Department of Health and the Welsh Assembly Government.

1.6 Other relevant documents

This guideline is intended to complement other existing and proposed works of relevance, including related NICE guidance:

- clinical guidelines
  - *Referral Advice* (2001)[11]
- technology appraisals (TAs)
  - *Frequency of Application of Topical Corticosteroids for Atopic Eczema* (2004)[12]
  - *Tacrolimus and Pimecrolimus for Atopic Eczema* (2004).[13]

1.7 Guideline methodology

This guideline was developed in accordance with the NICE guideline development process outlined in the 2005 technical manual[14] and the 2006 and 2007 editions of the *Guidelines Manual*.[15,16] Table 1.1 summarises the key stages of the guideline development process and which version of the process was followed for each stage.

Table 1.1 Stages in the NICE guideline development process and the versions followed at each stage

Stage	2005 version[14]	2006 version[15]	2007 version[16]
Scoping the guideline (determining what the guideline would and would not cover)	✓		
Preparing the work plan (agreeing timelines, milestones, GDG constitution, etc.)	✓		
Forming and running the GDG	✓		
Developing clinical questions	✓		
Identifying the evidence		✓	
Reviewing and grading the evidence		✓	
Incorporating health economics		✓	
Making group decisions and reaching consensus			✓
Linking guidance to other NICE guidance			✓
Creating guideline recommendations			✓
Developing clinical audit criteria			✓
Writing the guideline			✓
Validation (stakeholder consultation on the draft guideline)			✓
Declaration of interests[a]	✓	✓	✓

[a] The process for declaring interests was extended in November 2006 to cover NCC-WCH staff and to include personal family interests.

Literature search strategy

Initial scoping searches were executed to identify relevant guidelines (local, national and international) produced by other development groups. The reference lists in these guidelines were checked against subsequent searches to identify missing evidence.

Relevant published evidence to inform the guideline development process and answer the clinical questions was identified by systematic search strategies. The questions are presented in Appendix B. Additionally, stakeholder organisations were invited to submit evidence for consideration by the GDG provided it was relevant to the topics included in the scope and of equivalent or better quality than evidence identified by the search strategies.

Systematic searches to answer the clinical questions formulated and agreed by the GDG were executed using the following databases via the 'Ovid' platform: Medline (1966 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (1982 onwards), and PsycINFO (1967 onwards). The most recent search conducted for the three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects) was Quarter 1, 2007. The Allied and Complementary Medicine (AMED) database was searched from 1985 onwards for the clinical questions relating to diagnosis, trigger factors, complementary therapies and education (questions 1, 3, 4, 18–20 and 32 in Appendix B). Searches to identify economic studies were undertaken using the above databases and the NHS Economic Evaluations Database (NHS EED).

Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific. Language restrictions were not applied to searches, although publications in languages other than English were not appraised. Both generic and specially developed methodological search filters were used appropriately.

There was no systematic attempt to search grey literature (conferences, abstracts, theses and unpublished trials). Hand searching of journals not indexed on the databases was not undertaken.

Towards the end of the guideline development process searches were updated and re-executed, thereby including evidence published and included in the databases up to 21 March 2007.

Evidence published after this date has not been included in the guideline. This date should be considered the starting point for searching for new evidence for future updates to this guideline.

Further details of the search strategies, including the methodological filters employed, are provided on the accompanying CD-ROM.

Appraisal and synthesis of clinical effectiveness evidence

Evidence relating to clinical effectiveness was reviewed using established guides,[17-23] and classified using the established hierarchical system presented in Table 1.2.[15] This system reflects the susceptibility to bias that is inherent in particular study designs.

Table 1.2 Levels of evidence for intervention studies

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

The type of clinical question dictates the highest level of evidence that may be sought. In assessing the quality of the evidence, each study receives a quality rating coded as '++', '+' or '−'. For issues of therapy or treatment, the highest possible evidence level (EL) is a well-conducted systematic review or meta-analysis of randomised controlled trials (RCTs; EL = 1++) or an individual RCT (EL = 1+). Studies of poor quality are rated as '−'. Usually, studies rated as '−' should not be used as a basis for making a recommendation, but they can be used to inform recommendations. For issues of prognosis, the highest possible level of evidence is a cohort study (EL = 2). A level of evidence was assigned to each study, and to the body of evidence for each question.

For each clinical question, the highest available level of evidence was selected. Where appropriate, for example, if a systematic review, meta-analysis or RCT existed in relation to a question, studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs did not exist, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the efficacy (accuracy) of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of patients and the outcome of disease was required, evidence from RCTs or cohort studies was optimal. For studies evaluating the accuracy of a diagnostic test, sensitivity, specificity and positive and negative predictive values (PPVs and NPVs) were calculated or quoted where possible (see Table 1.3).

Table 1.3 '2 × 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	Reference standard negative	Total
Test positive	a (true positive)	b (false positive)	a+b
Test negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d = N (total number of tests in study)

Sensitivity = a/(a+c), specificity = d/(b+d), PPV = a/(a+b), NPV = d/(c+d)

The system described above covers studies of treatment effectiveness. However, it is less appropriate for studies reporting accuracy of diagnostic tests. In the absence of a validated ranking system for this type of test, NICE has developed a hierarchy of evidence that takes into account the various factors likely to affect the validity of these studies (see Table 1.4).[15]

Table 1.4 Levels of evidence for studies of the accuracy of diagnostics tests

Level	Type of evidence
Ia	Systematic reviews (with homogeneity)[a] of level-1 studies[b]
Ib	Level-1 studies[b]
II	Level-2 studies[c]; systematic reviews of level-2 studies
III	Level-3 studies[d]; systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

[a] Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

[b] Level-1 studies are studies that use a blind comparison of the test with a validated reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply.

[c] Level-2 studies are studies that have only one of the following:
- narrow population (the sample does not reflect the population to whom the test would apply)
- use a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- the comparison between the test and reference standard is not blind
- case–control studies.

[d] Level-3 studies are studies that have at least two or three of the features listed above.

Clinical evidence for individual studies was extracted into evidence tables (included on the accompanying CD-ROM) and a brief summary of each study was included in the guideline text. The body of evidence identified for each clinical question was synthesised qualitatively in clinical evidence statements that accurately reflected the evidence. Lists of excluded studies for each clinical question are provided on the CD-ROM. Quantitative synthesis (meta-analysis) was not performed for this guideline because there were no clinical questions for which sufficient numbers of similar studies were identified to merit such analysis.

Specific considerations for this guideline

While the scope of this guideline relates specifically to children aged 0–12 years, it was anticipated that some evidence relevant to this guideline would include people over the age of 12 years. Studies involving people older than 12 years were excluded in the first instance unless results were presented separately for children in the age range 0–12 years. Similarly, any studies that included people with skin conditions other than atopic eczema and did not present results separately for people with atopic eczema were excluded initially. Where initial searches did not identify any studies relating to the specific age group and condition as defined in the scope, the GDG considered whether it was appropriate to review evidence from older children or adults or evidence relating to other skin conditions with a view to extrapolating from such evidence to formulate recommendations for clinical care of children with atopic eczema.

The NICE technology appraisals (TAs) *Frequency of Application of Topical Corticosteroids for Atopic Eczema* (2004)[12] and *Tacrolimus and Pimecrolimus for Atopic Eczema* (2004)[13] were not updated within this guideline because they cover both adults and children.

One of the GDG's clinical questions was designed to identify management strategies appropriate for different ages and cultural groups (see Appendix B). No specific search was undertaken for this question, and evidence identified in relation to different ages or cultural groups was considered systematically under each of the other clinical questions.

For this guideline, the effectiveness of interventions has been assessed against the following outcome domains:

- disease activity, including severity, frequency and duration of flares, itching and scratching
- disease impact, including quality of life and sleep disturbance

- disease management, including children's and parents' knowledge about the disease and adherence to therapy
- laboratory markers, including serum cortisol levels, transepidermal water loss, skin thickness, inflammatory markers and immunoglobulin E (IgE) levels.

Health economics considerations

Cost-effectiveness issues were considered systematically for every clinical question except where the use of healthcare resources was not the focus of the question (diagnostic criteria, epidemiology and information/support) and the issues were summarised in the guideline text. The aims of the economic input to the guideline were to inform the GDG of potential economic issues relating to atopic eczema in children, and to ensure that recommendations represented cost-effective use of healthcare resources.

The GDG identified guideline topics that might benefit from economic analysis and sought to identify relevant economic evidence, although no published evidence was identified for this guideline. Had any such evidence been identified it would have been assessed using a quality assessment checklist based on good practice in decision-analytic modelling[24] (because no standard system of grading the quality of economic evaluations exists).

Health economic considerations were aided by original economic analysis undertaken as part of the development of the guideline where robust clinical effectiveness data were available and UK-based cost data could be obtained. For this guideline the only such areas were those relating to education and adherence to therapy (Chapter 8). The results of the economic analysis are summarised briefly in the guideline text, and a more detailed description of the methods is presented in Appendix D.

GDG interpretation of the evidence and formulation of recommendations

For each clinical question, recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the GDG to agree clinical and cost-effectiveness evidence statements. Statements summarising the GDG's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared. In areas where no substantial clinical research evidence was identified, the GDG considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions) was considered was based on GDG consensus in relation to the likely cost-effectiveness implications of the recommendations. The GDG also identified areas where evidence to answer their clinical questions was lacking and used this information to draft recommendations for future research.

Towards the end of the guideline development process formal consensus methods were used to consider all the clinical care recommendations and research recommendations that had been drafted previously. The method used to agree the wording of recommendations was essentially a modified Delphi technique in which each GDG member submitted an electronic form indicating their level of agreement with each draft recommendation and providing suggestions for changes where appropriate. All recommendations for which at least one GDG member indicated any level of disagreement were discussed at a subsequent GDG meeting, and the final wording was agreed following discussion of the relevant issues.

The GDG identified eleven key priorities for implementation (key recommendations), which were those recommendations expected to have the biggest impact on patients' care and patients' outcomes in the NHS as a whole. The key priorities were selected using a variant of the nominal group technique. Each GDG member submitted an electronic form indicating their top ten recommendations in order of priority. The GDG members' votes were collated and a shortlist of priority recommendations was obtained by including all recommendations that had been voted for by at least three GDG members plus any other recommendations that had been chosen as the top priority by at least one GDG member. The shortlisting procedure was determined on pragmatic grounds to limit the number of recommendations to that which could feasibly be considered at the next GDG meeting. The shortlisted recommendations were discussed at subsequent GDG meetings where further rounds of voting took place to eliminate all but the

top eleven recommendations (for example, by excluding recommendations that covered important aspects of the management of atopic eczema in children but which were thought to reflect current practice).

The GDG also identified five key priorities for research which were the most important research recommendations, again using a variant of the nominal group technique. Each GDG member submitted an electronic form indicating their top five research recommendations in order of priority. The GDG members' votes were collated and a shortlist of priority recommendations was obtained using exactly the same criteria that were used to shortlist recommendations for clinical care. The shortlisted recommendations were discussed at a GDG meeting and another round of voting took place to eliminate all but the top five research recommendations.

Stakeholder involvement in the guideline development process

Registered stakeholder organisations were invited to comment on the scope of the guideline during the scoping stage of development and on the evidence and recommendations in the validation stage (see Table 1.1).

The GDG has carefully considered and responded to all of the comments received from stakeholders during the consultation periods. The comments and responses, which were reviewed independently by a Guidelines Review Panel convened by NICE, are published on the NICE website.

1.8 Schedule for updating the guideline

Clinical guidelines commissioned by NICE are published with a review date 4 years from the date of publication. Reviewing may begin earlier than 4 years if significant evidence that affects guideline recommendations is identified sooner. The updated guideline will be available within 2 years of the start of the review process.

2 Summary of recommendations and treatment algorithm

2.1 Key priorities for implementation (key recommendations)

Chapter 4 Assessment of severity, psychological and psychosocial wellbeing and quality of life

Healthcare professionals should adopt a holistic approach when assessing a child's atopic eczema at each consultation, taking into account the severity of the atopic eczema and the child's quality of life, including everyday activities and sleep, and psychosocial wellbeing (see Table 4.4). There is not necessarily a direct relationship between the severity of the atopic eczema and the impact of the atopic eczema on quality of life.

Table 4.4 Holistic assessment

Skin/physical severity		Impact on quality of life and psychosocial wellbeing	
Clear	Normal skin, no evidence of active atopic eczema	None	No impact on quality of life
Mild	Areas of dry skin, infrequent itching (with or without small areas of redness)	Mild	Little impact on everyday activities, sleep and psychosocial wellbeing
Moderate	Areas of dry skin, frequent itching, redness (with or without excoriation and localised skin thickening)	Moderate	Moderate impact on everyday activities and psychosocial wellbeing, frequently disturbed sleep
Severe	Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation)	Severe	Severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep

Chapter 6 Identification and management of trigger factors

When clinically assessing children with atopic eczema, healthcare professionals should seek to identify potential trigger factors including:

- irritants, for example soaps and detergents (including shampoos, bubble baths, shower gels and washing-up liquids)
- skin infections
- contact allergens
- food allergens
- inhalant allergens.

Healthcare professionals should consider a diagnosis of food allergy in children with atopic eczema who have reacted previously to a food with immediate symptoms, or in infants and young children with moderate or severe atopic eczema that has not been controlled by optimum management, particularly if associated with gut dysmotility (colic, vomiting, altered bowel habit) or failure to thrive.

Chapter 7 Treatment

Stepped approach to management

Healthcare professionals should use a stepped approach for managing atopic eczema in children. This means tailoring the treatment step to the severity of the atopic eczema. Emollients should form the basis of atopic eczema management and should always be used, even when the atopic eczema is clear. Management can then be stepped up or down, according to the severity of symptoms, with the addition of the other treatments listed in Table 7.4.

Table 7.4 Treatment options

Mild atopic eczema	Moderate atopic eczema	Severe atopic eczema
Emollients	Emollients	Emollients
Mild potency topical corticosteroids	Moderate potency topical corticosteroids	Potent topical corticosteroids
	Topical calcineurin inhibitors	Topical calcineurin inhibitors
	Bandages	Bandages
		Phototherapy
		Systemic therapy

Healthcare professionals should offer children with atopic eczema and their parents or carers information on how to recognise flares of atopic eczema (increased dryness, itching, redness, swelling and general irritability). They should give clear instructions on how to manage flares according to the stepped-care plan, and prescribe treatments that allow children and their parents or carers to follow this plan.

Emollients

Healthcare professionals should offer children with atopic eczema a choice of unperfumed emollients to use every day for moisturising, washing and bathing. This should be suited to the child's needs and preferences, and may include a combination of products or one product for all purposes. Leave-on emollients should be prescribed in large quantities (250–500 g weekly) and easily available to use at nursery, pre-school or school.

Topical corticosteroids

The potency of topical corticosteroids should be tailored to the severity of the child's atopic eczema, which may vary according to body site. They should be used as follows:

- use mild potency for mild atopic eczema
- use moderate potency for moderate atopic eczema
- use potent for severe atopic eczema
- use mild potency for the face and neck, except for short-term (3–5 days) use of moderate potency for severe flares
- use moderate or potent preparations for short periods only (7–14 days) for flares in vulnerable sites such as axillae and groin
- do not use very potent preparations in children without specialist dermatological advice.

Treatment for infections associated with atopic eczema

Children with atopic eczema and their parents or carers should be offered information on how to recognise the symptoms and signs of bacterial infection with staphylococcus and/or streptococcus (weeping, pustules, crusts, atopic eczema failing to respond to therapy, rapidly worsening atopic eczema, fever and malaise). Healthcare professionals should provide clear information on how to access appropriate treatment when a child's atopic eczema becomes infected.

Children with atopic eczema and their parents or carers should be offered information on how to recognise eczema herpeticum. Signs of eczema herpeticum are:

- areas of rapidly worsening, painful eczema
- clustered blisters consistent with early-stage cold sores
- punched-out erosions (circular, depressed, ulcerated lesions) usually 1–3 mm that are uniform in appearance (these may coalesce to form larger areas of erosion with crusting)
- possible fever, lethargy or distress.

Chapter 8 Education and adherence to therapy

Healthcare professionals should spend time educating children with atopic eczema and their parents or carers about atopic eczema and its treatment. They should provide information in verbal and written forms, with practical demonstrations, and should cover:

- how much of the treatments to use
- how often to apply treatments
- when and how to step treatment up or down
- how to treat infected atopic eczema.

This should be reinforced at every consultation, addressing factors that affect adherence.

Chapter 10 Indications for referral

Referral for specialist dermatological advice is recommended for children with atopic eczema if:

- the diagnosis is, or has become, uncertain
- management has not controlled the atopic eczema satisfactorily based on a subjective assessment by the child, parent or carer (for example, the child is having 1–2 weeks of flares per month or is reacting adversely to many emollients)
- atopic eczema on the face has not responded to appropriate treatment
- the child or parent/carer may benefit from specialist advice on treatment application (for example, bandaging techniques)
- contact allergic dermatitis is suspected (for example, persistent atopic eczema or facial, eyelid or hand atopic eczema)
- the atopic eczema is giving rise to significant social or psychological problems for the child or parent/carer (for example, sleep disturbance, poor school attendance)
- atopic eczema is associated with severe and recurrent infections, especially deep abscesses or pneumonia.

2.2 Summary of recommendations

Chapter 3 Diagnosis

To aid management of atopic eczema in children, healthcare professionals should take detailed clinical and drug histories that include questions about:

- time of onset, pattern and severity of the atopic eczema
- response to previous and current treatments
- possible trigger factors (irritant and allergic)
- the impact of the atopic eczema on children and their parents or carers
- dietary history including any dietary manipulation
- growth and development
- personal and family history of atopic diseases.

Atopic eczema should be diagnosed when a child has an itchy skin condition plus three or more of the following:

- visible flexural dermatitis involving the skin creases, such as the bends of the elbows or behind the knees (or visible dermatitis on the cheeks and/or extensor areas in children aged 18 months or under)
- personal history of flexural dermatitis (or dermatitis on the cheeks and/or extensor areas in children aged 18 months or under)

- personal history of dry skin in the last 12 months
- personal history of asthma or allergic rhinitis (or history of atopic disease in a first-degree relative of children aged under 4 years)
- onset of signs and symptoms under the age of 2 years (this criterion should not be used in children aged under 4 years).

Healthcare professionals should be aware that in Asian, black Caribbean and black African children, atopic eczema can affect the extensor surfaces rather than the flexures, and discoid (circular) or follicular (around hair follicles) patterns may be more common.

Chapter 4 Assessment of severity, psychological and psychosocial wellbeing and quality of life

Healthcare professionals should adopt a holistic approach when assessing a child's atopic eczema at each consultation, taking into account the severity of the atopic eczema and the child's quality of life, including everyday activities and sleep, and psychosocial wellbeing (see Table 4.4). There is not necessarily a direct relationship between the severity of the atopic eczema and the impact of the atopic eczema on quality of life.

Table 4.4 Holistic assessment

Skin/physical severity		Impact on quality of life and psychosocial wellbeing	
Clear	Normal skin, no evidence of active atopic eczema	None	No impact on quality of life
Mild	Areas of dry skin, infrequent itching (with or without small areas of redness)	Mild	Little impact on everyday activities, sleep and psychosocial wellbeing
Moderate	Areas of dry skin, frequent itching, redness (with or without excoriation and localised skin thickening)	Moderate	Moderate impact on everyday activities and psychosocial wellbeing, frequently disturbed sleep
Severe	Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation)	Severe	Severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep

Healthcare professionals should explain the overall physical severity of a child's atopic eczema to the child and their parents or carers.

Healthcare professionals should be aware that areas of atopic eczema of differing severity can coexist in the same child. If this is the case, each area should be treated independently.

During an assessment of psychological and psychosocial wellbeing and quality of life, healthcare professionals should take into account the impact of atopic eczema on parents or carers as well as the child and provide appropriate advice and support.

Healthcare professionals should be aware that all categories of severity of atopic eczema, even mild, can have a negative impact on psychological and psychosocial wellbeing and quality of life. This should be taken into account when deciding on treatment strategies.

Healthcare professionals should consider using the following additional tools to provide objective measures of the severity of atopic eczema, quality of life and response to treatment:

- visual analogue scales (0–10) capturing the child's and/or parents' or carers' assessment of severity, itch and sleep loss over the previous 3 days and nights
- validated tools:
  - Patient-Oriented Eczema Measure (POEM) for severity
  - Children's Dermatology Life Quality Index (CDLQI), Infants' Dermatitis Quality of Life index (IDQoL) or Dermatitis Family Impact questionnaire (DFI) for quality of life.

Chapter 5 Epidemiology

Healthcare professionals should inform children with atopic eczema and their parents or carers that the condition often improves with time, but that not all children will grow out of atopic eczema and it may get worse in teenage or adult life.

Healthcare professionals should inform children with atopic eczema and their parents or carers that children with atopic eczema can often develop asthma and/or allergic rhinitis and that sometimes food allergy is associated with atopic eczema, particularly in very young children.

Chapter 6 Identification and management of trigger factors

When clinically assessing children with atopic eczema, healthcare professionals should seek to identify potential trigger factors including:

- irritants, for example soaps and detergents (including shampoos, bubble baths, shower gels and washing-up liquids)
- skin infections
- contact allergens
- food allergens
- inhalant allergens.

Healthcare professionals should consider a diagnosis of food allergy in children with atopic eczema who have reacted previously to a food with immediate symptoms, or in infants and young children with moderate or severe atopic eczema that has not been controlled by optimum management, particularly if associated with gut dysmotility (colic, vomiting, altered bowel habit) or failure to thrive.

Healthcare professionals should consider a diagnosis of inhalant allergy in children with seasonal flares of atopic eczema, children with atopic eczema associated with asthma or allergic rhinitis, and children aged 3 years or over with atopic eczema on the face, particularly around the eyes.

Healthcare professionals should consider a diagnosis of allergic contact dermatitis in children with an exacerbation of previously controlled atopic eczema or with reactions to topical treatments.

Healthcare professionals should reassure children with mild atopic eczema and their parents or carers that most children with mild atopic eczema do not need to have tests for allergies.

Healthcare professionals should advise children with atopic eczema and their parents or carers not to undergo high street or internet allergy tests because there is no evidence of their value in the management of atopic eczema.

Healthcare professionals should offer a 6–8 week trial of an extensively hydrolysed protein formula or amino acid formula in place of cow's milk formula for bottle-fed infants aged under 6 months with moderate or severe atopic eczema that has not been controlled by optimal treatment with emollients and mild topical corticosteroids.

Healthcare professionals should refer children with atopic eczema who follow a cow's milk-free diet for longer than 8 weeks for specialist dietary advice.

Diets based on unmodified proteins of other species' milk (for example, goat's milk, sheep's milk) or partially hydrolysed formulas should not be used in children with atopic eczema for the management of suspected cow's milk allergy. Diets including soya protein can be offered to children aged 6 months or over with specialist dietary advice.

Healthcare professionals should inform women who are breastfeeding children with atopic eczema that it is not known whether altering the mother's diet is effective in reducing the severity of the condition. A trial of an allergen-specific exclusion diet should be considered under dietary supervision if food allergy is strongly suspected.

Healthcare professionals should inform children with atopic eczema and their parents or carers that it is unclear what role factors such as stress, humidity or extremes of temperature have in causing flares of atopic eczema. These factors should be avoided where possible.

Chapter 7 Treatment

Stepped approach to management

Healthcare professionals should use a stepped approach for managing atopic eczema in children. This means tailoring the treatment step to the severity of the atopic eczema. Emollients should form the basis of atopic eczema management and should always be used, even when the atopic eczema is clear. Management can then be stepped up or down, according to the severity of symptoms, with the addition of the other treatments listed in Table 7.4.

Table 7.4 Treatment options

Mild atopic eczema	Moderate atopic eczema	Severe atopic eczema
Emollients	Emollients	Emollients
Mild potency topical corticosteroids	Moderate potency topical corticosteroids	Potent topical corticosteroids
	Topical calcineurin inhibitors	Topical calcineurin inhibitors
	Bandages	Bandages
		Phototherapy
		Systemic therapy

Healthcare professionals should offer children with atopic eczema and their parents or carers information on how to recognise flares of atopic eczema (increased dryness, itching, redness, swelling and general irritability). They should give clear instructions on how to manage flares according to the stepped-care plan, and prescribe treatments that allow children and their parents or carers to follow this plan.

Treatment for flares of atopic eczema in children should be started as soon as signs and symptoms appear and continued for approximately 48 hours after symptoms subside.

Emollients

Healthcare professionals should offer children with atopic eczema a choice of unperfumed emollients to use every day for moisturising, washing and bathing. This should be suited to the child's needs and preferences, and may include a combination of products or one product for all purposes. Leave-on emollients should be prescribed in large quantities (250–500 g weekly) and easily available to use at nursery, pre-school or school.

Healthcare professionals should inform children with atopic eczema and their parents or carers that they should use emollients in larger amounts and more often than other treatments. Emollients should be used on the whole body both when the atopic eczema is clear and while using all other treatments.

Healthcare professionals should inform children with atopic eczema and their parents or carers that they should use emollients and/or emollient wash products instead of soaps and detergent-based wash products.

Healthcare professionals should advise parents or carers of children aged under 12 months with atopic eczema to use emollients and/or emollient wash products instead of shampoos for the child. If shampoo is used for older children with atopic eczema it should be unperfumed and ideally labelled as being suitable for eczema; washing the hair in bath water should be avoided.

Healthcare professionals should show children with atopic eczema and their parents or carers how to apply emollients, including how to smooth emollients onto the skin rather than rubbing them in.

Healthcare professionals should offer an alternative emollient if a particular emollient causes irritation or is not acceptable to a child with atopic eczema.

Healthcare professionals should review repeat prescriptions of individual products and combinations of products with children with atopic eczema and their parents or carers at least once a year to ensure that therapy remains optimal.

Where emollients (excluding bath emollients) and other topical products are used at the same time of day to treat atopic eczema in children, the different products should ideally be applied one at a time with several minutes between applications where practical. The preferences of the child and parents or carers should determine which product should be applied first.

Topical corticosteroids

Healthcare professionals should discuss the benefits and harms of treatment with topical corticosteroids with children with atopic eczema and their parents or carers, emphasising that the benefits outweigh possible harms when they are applied correctly.

The potency of topical corticosteroids should be tailored to the severity of the child's atopic eczema, which may vary according to body site. They should be used as follows:

- use mild potency for mild atopic eczema
- use moderate potency for moderate atopic eczema
- use potent for severe atopic eczema
- use mild potency for the face and neck, except for short-term (3–5 days) use of moderate potency for severe flares
- use moderate or potent preparations for short periods only (7–14 days) for flares in vulnerable sites such as axillae and groin
- do not use very potent preparations in children without specialist dermatological advice.

It is recommended that topical corticosteroids for atopic eczema should be prescribed for application only once or twice daily.*

It is recommended that where more than one alternative topical corticosteroid is considered clinically appropriate within a potency class, the drug with the lowest acquisition cost should be prescribed, taking into account pack size and frequency of application.*

Healthcare professionals should inform children with atopic eczema and their parents or carers that they should only apply topical corticosteroids to areas of active atopic eczema (or eczema that has been active within the past 48 hours), which may include areas of broken skin.

Healthcare professionals should exclude secondary bacterial or viral infection if a mild or moderately potent topical corticosteroid has not controlled the atopic eczema within 7–14 days. In children aged 12 months or over, potent topical corticosteroids should then be used for as short a time as possible and in any case no longer than 14 days. They should not be used on the face or neck. If this treatment does not control the atopic eczema, the diagnosis should be reviewed and the child referred for specialist dermatological advice.

Potent topical corticosteroids should not be used in children aged under 12 months without specialist dermatological supervision.

Healthcare professionals who dispense topical corticosteroids should apply labels stating the potency class of the preparations to the container (for example, the tube), not the outer packaging.

Healthcare professionals should consider treating problem areas of atopic eczema with topical corticosteroids for two consecutive days per week to prevent flares, instead of treating flares as they arise, in children with frequent flares (two or three per month), once the eczema has been controlled. This strategy should be reviewed within 3–6 months to assess effectiveness.

A different topical corticosteroid of the same potency should be considered as an alternative to stepping up treatment if tachyphylaxis to a topical corticosteroid is suspected in children with atopic eczema.

* These recommendations are taken from 'Frequency of application of topical corticosteroids for atopic eczema' (NICE technology appraisal guidance 81). They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

Topical calcineurin inhibitors

Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity.*

Topical tacrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged 2 years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.*

Pimecrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged 2–16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.*

For the purposes of this guidance, atopic eczema that has not been controlled by topical corticosteroids refers to disease that has not shown a satisfactory clinical response to adequate use of the maximum strength and potency that is appropriate for the patient's age and the area being treated.*

It is recommended that treatment with tacrolimus or pimecrolimus be initiated only by physicians (including general practitioners) with a special interest and experience in dermatology, and only after careful discussion with the patient about the potential risks and benefits of all appropriate second-line treatment options.*

Healthcare professionals should explain to children with atopic eczema and their parents or carers that they should only apply topical calcineurin inhibitors to areas of active atopic eczema, which may include areas of broken skin.

Topical calcineurin inhibitors should not be used under occlusion (bandages and dressings) for treating atopic eczema in children without specialist dermatological advice.

For facial atopic eczema in children that requires long-term or frequent use of mild topical corticosteroids, consider stepping up treatment to topical calcineurin inhibitors.

Dry bandages and medicated dressings (including wet wrap therapy)

Occlusive medicated dressings and dry bandages should not be used to treat infected atopic eczema in children.

Localised medicated dressings or dry bandages can be used with emollients as a treatment for areas of chronic lichenified (localised skin thickening) atopic eczema in children.

Localised medicated dressings or dry bandages with emollients and topical corticosteroids can be used for short-term treatment of flares (7–14 days) or areas of chronic lichenified atopic eczema in children.

Whole-body (limbs and trunk) occlusive dressings (including wet wrap therapy) and whole-body dry bandages (including tubular bandages and garments) should not be used as first-line treatment for atopic eczema in children and should only be initiated by a healthcare professional trained in their use.

Whole-body (limbs and trunk) occlusive dressings (including wet wrap therapy) with topical corticosteroids should only be used to treat atopic eczema in children for 7–14 days (or for longer with specialist dermatological advice), but can be continued with emollients alone until the atopic eczema is controlled.

Antihistamines and antipruritics

Oral antihistamines should not be used routinely in the management of atopic eczema in children.

Healthcare professionals should offer a 1 month trial of a non-sedating antihistamine to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria. Treatment can be continued, if successful, while symptoms persist, and should be reviewed every 3 months.

* These recommendations are taken from 'Tacrolimus and pimecrolimus for atopic eczema' (NICE technology appraisal guidance 82). They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

Healthcare professionals should offer a 7–14 day trial of an age-appropriate sedating antihistamine to children aged 6 months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers. This treatment can be repeated during subsequent flares if successful.

Treatment for infections associated with atopic eczema

Children with atopic eczema and their parents or carers should be offered information on how to recognise the symptoms and signs of bacterial infection with staphylococcus and/or streptococcus (weeping, pustules, crusts, atopic eczema failing to respond to therapy, rapidly worsening atopic eczema, fever and malaise). Healthcare professionals should provide clear information on how to access appropriate treatment when a child's atopic eczema becomes infected.

Children with atopic eczema and their parents or carers should be informed that they should obtain new supplies of topical atopic eczema medications after treatment for infected atopic eczema because products in open containers can become contaminated with microorganisms and act as a source of infection.

Healthcare professionals should only take swabs from infected lesions of atopic eczema in children if they suspect microorganisms other than *Staphylococcus aureus* to be present, or if they think antibiotic resistance is relevant.

Systemic antibiotics that are active against *Staphylococcus aureus* and streptococcus should be used to treat widespread bacterial infections of atopic eczema in children for 1–2 weeks according to clinical response.

Flucloxacillin should be used as the first-line treatment for bacterial infections in children with atopic eczema for both *Staphylococcus aureus* and streptococcal infections. Erythromycin should be used in children who are allergic to flucloxacillin or in the case of flucloxacillin resistance. Clarithromycin should be used if erythromycin is not well tolerated.

The use of topical antibiotics in children with atopic eczema, including those combined with topical corticosteroids, should be reserved for cases of clinical infection in localised areas and used for no longer than 2 weeks.

Antiseptics such as triclosan or chlorhexidine should be used, at appropriate dilutions, as adjunct therapy to decrease bacterial load in children who have recurrent infected atopic eczema. Long-term use should be avoided.

Healthcare professionals should consider infection with herpes simplex (cold sore) virus if a child's infected atopic eczema fails to respond to treatment with antibiotics and an appropriate topical corticosteroid.

If a child with atopic eczema has a lesion on the skin suspected to be herpes simplex virus, treatment with oral aciclovir should be started even if the infection is localised.

If eczema herpeticum (widespread herpes simplex virus) is suspected in a child with atopic eczema, treatment with systemic aciclovir should be started immediately and the child should be referred for same-day specialist dermatological advice. If secondary bacterial infection is also suspected, treatment with appropriate systemic antibiotics should also be started.

If eczema herpeticum involves the skin around the eyes, the child should be treated with systemic aciclovir and should be referred for same-day ophthalmological and dermatological advice.

Children with atopic eczema and their parents or carers should be offered information on how to recognise eczema herpeticum. Signs of eczema herpeticum are:

- areas of rapidly worsening, painful eczema
- clustered blisters consistent with early-stage cold sores
- punched-out erosions (circular, depressed, ulcerated lesions) usually 1–3 mm that are uniform in appearance (these may coalesce to form larger areas of erosion with crusting)
- possible fever, lethargy or distress.

Phototherapy and systemic treatments

Healthcare professionals should consider phototherapy or systemic treatments for the treatment of severe atopic eczema in children when other management options have failed or are inappropriate and where there is a significant negative impact on quality of life. Treatment should be undertaken only under specialist dermatological supervision by staff who are experienced in dealing with children.

Phototherapy or systemic treatments should only be initiated in children with atopic eczema after assessment and documentation of severity of atopic eczema and quality of life.

Complementary therapies

Children with atopic eczema and their parents or carers should be informed that the effectiveness and safety of complementary therapies such as homeopathy, herbal medicine, massage and food supplements for the management of atopic eczema have not yet been adequately assessed in clinical studies.

Children with atopic eczema and their parents or carers should be informed that:

- they should be cautious with the use of herbal medicines in children and be wary of any herbal product that is not labelled in English or does not come with information about safe usage*
- topical corticosteroids are deliberately added to some herbal products intended for use in children with atopic eczema*
- liver toxicity has been associated with the use of some Chinese herbal medicines intended to treat atopic eczema.

Children with atopic eczema and their parents or carers should be asked to inform their healthcare professionals if they are using or intend to use complementary therapies.

Children with atopic eczema and their parents or carers should be informed that if they plan to use complementary therapies, they should keep using emollients as well.

Children with atopic eczema and their parents or carers should be advised that regular massage with emollients may improve the atopic eczema.

Chapter 8 Education and adherence to therapy

Healthcare professionals should spend time educating children with atopic eczema and their parents or carers about atopic eczema and its treatment. They should provide information in verbal and written forms, with practical demonstrations, and should cover:

- how much of the treatments to use
- how often to apply treatments
- when and how to step treatment up or down
- how to treat infected atopic eczema.

This should be reinforced at every consultation, addressing factors that affect adherence.

When discussing treatment options with children with atopic eczema and their parents and carers, healthcare professionals should tailor the information they provide to suit the child's cultural practices relating to skin care (including oiling the skin) and the way they bathe.

Healthcare professionals should inform children with atopic eczema and their parents or carers that atopic eczema may temporarily cause the skin to become lighter or darker.

Chapter 10 Indications for referral

Immediate (same-day) referral for specialist dermatological advice is recommended if eczema herpeticum is suspected.

* See 'Using herbal medicines: advice to consumers'. July 2006, MHRA, www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=661.

Urgent (within 2 weeks) referral for specialist dermatological advice is recommended for children with atopic eczema if:

- the atopic eczema is severe and has not responded to optimum topical therapy after 1 week
- treatment of bacterially infected atopic eczema has failed.

Referral for specialist dermatological advice is recommended for children with atopic eczema if:

- the diagnosis is, or has become, uncertain
- management has not controlled the atopic eczema satisfactorily based on a subjective assessment by the child, parent or carer (for example, the child is having 1–2 weeks of flares per month or is reacting adversely to many emollients)
- atopic eczema on the face has not responded to appropriate treatment
- the child or parent/carer may benefit from specialist advice on treatment application (for example, bandaging techniques)
- contact allergic dermatitis is suspected (for example, persistent atopic eczema or facial, eyelid or hand atopic eczema)
- the atopic eczema is giving rise to significant social or psychological problems for the child or parent/carer (for example, sleep disturbance, poor school attendance)
- atopic eczema is associated with severe and recurrent infections, especially deep abscesses or pneumonia.

Children with atopic eczema that has responded to optimum management but for whom the impact of the atopic eczema on quality of life and psychosocial wellbeing has not improved should be referred for psychological advice.

Children with moderate or severe atopic eczema and suspected food allergy should be referred for specialist investigation and management of the atopic eczema and allergy.

Children with atopic eczema who fail to grow at the expected growth trajectory, as reflected by UK growth charts, should be referred for specialist advice relating to growth.

2.3 Key priorities for research

Infant feeding

What is the optimal feeding regimen in the first year of life for children with established atopic eczema?

Why this is important
Dietary manipulation has the potential to decrease disease severity in children with proven food allergy. A study is needed to explore the potential benefits and harms of delaying the introduction of allergenic foods such as milk, egg and peanuts in infants with early signs of atopic eczema to assess the potential impact on atopic eczema severity and the subsequent development of food allergy, asthma and allergic rhinitis.

Prevention of flares

Which are the best, most cost-effective treatment strategies for managing and preventing flares in children with atopic eczema?

Why this is important
Atopic eczema is usually an episodic disease of exacerbation (flares) and remissions, except for severe cases where it may be continuous (2–6% of cases). Flares may occur as frequently as two or three times per month and have a very negative effect on quality of life. They are time-consuming and expensive to treat. There is limited evidence suggesting that strategies to prevent flares can reduce the number, frequency and severity of flares and the amount of treatment required. Identifying good strategies would improve patient care and quality of life, and free up NHS resources. Strategies that could be considered in this research include continuous versus intermittent topical treatments or combinations of products such as topical corticosteroids and topical calcineurin inhibitors.

Early intervention

What effect does improving the control of atopic eczema in the first year of life have on the long-term control and severity of atopic eczema and the subsequent development and severity of food allergy, asthma and allergic rhinitis?

Why this is important
Uncontrolled atopic eczema in children may progress to chronic disease involving the production of auto-immune antibodies to the skin. Early intervention to restore the defective skin barrier might alter the course of atopic eczema by preventing allergen penetration. A systematic review is needed to evaluate the available evidence on these factors. The results should feed in to the design of a large randomised controlled trial investigating the long-term effect of controlling atopic eczema in the first year of life. Early effective treatment to control atopic eczema and the development of other atopic conditions would be extremely cost-effective, have a major impact on service provision and improve the quality of life of children with atopic eczema and their parents and carers.

Adverse effects of topical corticosteroids

What are the long-term effects (when used for between 1 and 3 years) of typical use of topical corticosteroids in children with atopic eczema?

Why this is important
Around 70–80% of parents and carers of children with atopic eczema are concerned about the side effects of topical corticosteroids and this often prevents adherence to therapy (at least 25% of parents and carers report non-usage because of anxiety). Despite the fact that topical corticosteroids have been in clinical use since 1962, there are limited data on their long-term effects (greater than a few weeks) on skin thickness, hypothalamic–pituitary–adrenal (HPA) axis suppression and other side effects. Clinical consensus suggests that long-term usage, within clinically recommended dosages, appears to be safe; research confirming this would greatly improve adherence to therapy and clinical outcomes, and reduce parental anxiety. The research could include comparisons between children who use topical corticosteroids for shorter and longer periods, and with those who use other topical preparations such as emollients and topical calcineurin inhibitors.

Education and adherence to therapy

How effective and cost-effective are different models of educational programmes in the early management of atopic eczema in children, in terms of improving adherence to therapy and patient outcomes such as disease severity and quality of life?

Why this is important
Atopic eczema is a common childhood disease affecting one in five children in the UK. Effective therapy improves quality of life for children with atopic eczema and their parents and carers, and can be provided for over 80% of children with atopic eczema in a primary care setting. It is known that a lack of education about therapy leads to poor adherence, and consequently to treatment failure.

2.4 Summary of research recommendations

Chapter 3 Diagnosis

What is the validity of currently used diagnostic criteria for atopic eczema when used in different ethnic groups?

Why this is important
Atopic eczema has a different clinical presentation in some ethnic groups with greater lichenification and papulation and a predilection for extensor rather than flexural areas. The UK diagnostic criteria have not been tested extensively in non-white ethnic groups in the UK.

Chapter 4 Assessment of severity, psychological and psychosocial wellbeing and quality of life

Does the use of severity tools in the assessment of atopic eczema in children in routine practice improve clinical management and outcome (aiding decisions on treatment strategies, increasing clinical response) and is this a cost-effective use of clinical time?

Why this is important
Assessing the severity of eczema is very difficult to do but is essential in guiding management of the disease. Easy-to-use validated methods are required in order to aid clinical management in a cost-effective way.

What is the optimal method (in terms of ease of use, accuracy and sensitivity) of measuring the severity of atopic eczema in children in routine clinical practice?

Why this is important
The majority of instruments for measuring the severity of atopic eczema in children have been developed and validated for clinical research rather than for routine clinical practice. There is a need for studies comparing the available measurement instruments in routine clinical practice where the spectrum of disease severity and time available for measurements may differ significantly from the research setting.

Which psychological and quality of life scales are the most appropriate for use in clinical practice in children with atopic eczema in terms of guiding management or for outcomes of treatment and is their use effective and cost-effective?

Why this is important
Eczema can have a detrimental psychological effect on children and also impair their quality of life. Measurement tools can ascertain the level of effect and whether or not treatment improves it but many are too cumbersome and time-consuming to use in a clinical setting. Research is required to ascertain the usefulness and cost-effectiveness (clinical time) of using such validated tool in a clinical setting and which are quick and simple to use, giving reproducible results.

Chapter 6 Identification and management of trigger factors

How effective and cost-effective is the use of house dust mite avoidance strategies in the treatment of childhood atopic eczema and which strategies, if any, are the most effective?

Why this is important
There are conflicting data on the effectiveness of using house dust mite avoidance strategies in the management of childhood atopic eczema. Many of the currently suggested techniques are time-consuming and expensive for parents/carers and it is important to establish their value.

When and how should children with atopic eczema be tested for allergies (skin prick tests, allergen-specific immunoglobulin E), and how can the diagnostic accuracy and effect on clinical outcomes of the tests be improved?

Why this is important
Parents and carers of children with atopic eczema often ask for allergy testing. However, there is confusion among clinicians about which tests are the most appropriate for different age groups. Interpretation of test results requires training and can be difficult because the diagnostic accuracy is uncertain; carrying out the tests is expensive and time-consuming and requires special training. The research should encompass clinical outcomes (for example, control of atopic eczema) in children who are diagnosed with allergies and undergo interventions to avoid exposure to relevant allergens. The results of the research will enable effective and cost-effective use of NHS resources.

How should exposure to pets be managed in children with atopic eczema; at what age does allergy occur and does tolerance develop?

Why this is important
Many children with atopic eczema show signs and symptoms of allergic reactions when in contact with animals such as cats, dogs and horses. However, clinical experience has found that

many people report tolerance of their own pet but not others and this tolerance may be lost when teenagers move away from home. In cases of extreme allergy, some practitioners recommend the removal of the pet, while others suggest limited 'managed' exposure. There is a single abstract report of children choosing their pet as one of their three most favourite items and the psychological distress of pet removal may not be justified. Clear guidance is needed on the correct management of pet allergy in children with atopic eczema.

What is the optimal feeding regimen in the first year of life for children with established atopic eczema?

Why this is important
Dietary manipulation has the potential to decrease disease severity in children with proven food allergy. A study is needed to explore the potential benefits and harms of delaying the introduction of allergenic foods such as milk, egg and peanuts in infants with early signs of atopic eczema to assess the potential impact on atopic eczema severity and the subsequent development of food allergy, asthma and allergic rhinitis.

Chapter 7 Treatment

Stepped approach to management

How should flares of atopic eczema be defined/recognised, what pattern do they take and how useful is this to clinical practice?

Why this is important
Atopic eczema is an episodic disease punctuated by flares and remissions in most cases. It is important to be able to recognise the onset of a flare for children and their parents so that treatment can be given promptly and effectively thus improving quality of life and care. It would also aid decisions on clinical treatment strategies and provide an effective outcome measure for research purposes.

Which are the best, most cost-effective treatment strategies for managing and preventing flares in children with atopic eczema?

Why this is important
Atopic eczema is usually an episodic disease of exacerbation (flares) and remissions, except for severe cases where it may be continuous (2–6% of cases). Flares may occur as frequently as two or three times per month and have a very negative effect on quality of life. They are time-consuming and expensive to treat. There is limited evidence suggesting that strategies to prevent flares can reduce the number, frequency and severity of flares and the amount of treatment required. Identifying good strategies would improve patient care and quality of life, and free up NHS resources. Strategies that could be considered in this research include continuous versus intermittent topical treatments or combinations of products such as topical corticosteroids and topical calcineurin inhibitors.

What effect does improving the control of atopic eczema in the first year of life have on the long-term control and severity of atopic eczema and the subsequent development and severity of food allergy, asthma and allergic rhinitis?

Why this is important
Uncontrolled atopic eczema in children may progress to chronic disease involving the production of auto-immune antibodies to the skin. Early intervention to restore the defective skin barrier might alter the course of atopic eczema by preventing allergen penetration. A systematic review is needed to evaluate the available evidence on these factors. The results should feed in to the design of a large randomised controlled trial investigating the long-term effect of controlling atopic eczema in the first year of life. Early effective treatment to control atopic eczema and the development of other atopic conditions would be extremely cost-effective, have a major impact on service provision and improve the quality of life of children with atopic eczema and their parents and carers.

Emollients

Which are the most effective and cost-effective combinations of emollient products to use for the treatment of childhood atopic eczema?

Why this is important
Most children with atopic eczema have a very dry skin and early treatment with emollients makes the skin less itchy, reducing the severity of the eczema. There are numerous types and formulations of emollients but little data to suggest how they can best be used in the most effective and cost-effective way.

Does the regular use of emollients reduce the severity and frequency of flares and the need for other topical agents in the treatment of atopic eczema in children?

Why this is important
Clinical consensus suggests that this is the case but there is little good evidence for this. Confirmation would help to encourage children and their parents to comply with therapy and reduce the need for other therapies, as well as improve their quality of life.

Topical corticosteroids

What are the long-term effects (when used for between 1 and 3 years) of typical use of topical corticosteroids in children with atopic eczema?

Why this is important
Around 70–80% of parents and carers of children with atopic eczema are concerned about the side effects of topical corticosteroids and this often prevents adherence to therapy (at least 25% of parents and carers report non-usage because of anxiety). Despite the fact that topical corticosteroids have been in clinical use since 1962, there are limited data on their long-term effects (greater than a few weeks) on skin thickness, hypothalamic–pituitary–adrenal (HPA) axis suppression and other side effects. Clinical consensus suggests that long-term usage, within clinically recommended dosages, appears to be safe; research confirming this would greatly improve adherence to therapy and clinical outcomes, and reduce parental anxiety. The research could include comparisons between children who use topical corticosteroids for shorter and longer periods, and with those who use other topical preparations such as emollients and topical calcineurin inhibitors.

What are the optimal treatment regimens for using topical corticosteroids in the treatment of atopic eczema in children?

Why this is important
Topical corticosteroids have been used since 1962, which predated modern randomised controlled trials (RCTs). High-quality comparative RCTs are required to provide data on the effectiveness and cost-effectiveness of various topical corticosteroids preparations in the treatment of atopic eczema in children.

Topical calcineurin inhibitors

What are the most effective, cost-effective and safe ways of using combinations of topical calcineurin inhibitors with topical corticosteroids of different potencies in the treatment of atopic eczema in children, with particular reference to areas of thin skin such as the face and flexures?

Why this is important
Topical calcineurin inhibitors and topical corticosteroids are often combined in clinical practice but high-quality data are required on their safety and effectiveness/cost-effectiveness in terms of clinical benefit.

What is the effectiveness and safety of using topical calcineurin inhibitors for treating children with atopic eczema in comparison with using different potencies of topical corticosteroids and does this differ in various body sites such as the face?

Why this is important
There are few direct comparative data on the use of topical calcineurin inhibitors, particularly pimecrolimus, in different body sites and in comparison with topical corticosteroids of different potencies. Long-term use of hydrocortisone on the face is more likely to cause cutaneous atrophy than when used in other sites and topical pimecrolimus appears to be a suitable alternative. High-quality RCTs would help to answer this question.

How effective/cost-effective and safe is the use of topical tacrolimus 0.1% ointment for treating children with atopic eczema?

Why this is important
At present topical tacrolimus 0.1% ointment is not licensed for use in children under 16 years. However, clinical consensus suggests that it may be a useful, safer and probably more cost-effective alternative to, for example, long-term potent topical corticosteroids or systemic therapies for children with chronic eczema unresponsive to the 0.03% preparation of topical tacrolimus. High-quality RCTs and safety studies are required to answer this question.

What are the optimal treatment durations when using topical pimecrolimus and tacrolimus in the treatment of children with atopic eczema?

Why this is important
The topical calcineurin inhibitor formulations are new and relatively expensive with optimal treatment duration strategies not yet established. High-quality RCTs would lead to more effective/cost-effective therapy and a better use of scarce resources.

How safe are topical calcineurin inhibitors for long-term therapy (1–3 years) in the treatment of atopic eczema in children?

Why this is important
Topical calcineurin inhibitors are new drugs and safety for longer term use is not yet established. Adequately powered long-term studies in relation to tacrolimus and pimecrolimus are needed.

Dry bandages and medicated dressings (including wet wrap therapy)

What are the benefits and harms of the different bandaging therapies (for example, wet, dry and medicated bandages) in the treatment of atopic eczema in children?

Why this is important
Bandages are widely used to treat atopic eczema in children and many different treatment regimens are used. These treatments are expensive and time-consuming but there are few data on their clinical and cost-effectiveness and safety. Good-quality RCTs are required to evaluate benefits and harms, in particular which children benefit from such therapy and how therapies should be used.

How effective, cost-effective and safe are wet wrap dressings with emollients alone or in combination with various potencies of topical corticosteroids, for the longer term management (greater than 5 days consecutively) of atopic eczema in children and how do they compare with the use of other topical therapies alone?

Why this is important
Wet wrap dressings, usually combined with topical corticosteroid preparations, can be very effective for short-term treatment of severe eczema, but because they increase steroid absorption there is a significant risk of HPA axis suppression after 5 days' use and an increased risk of skin infection. In clinical practice they are frequently used for periods longer than 5 days, with emollients alone or in combination with topical corticosteroids, often diluted. It is not known how safe, effective/cost-effective or practical they are for longer term management in comparison with using topical treatments alone.

How effective is the use of topical corticosteroids of different potencies or topical calcineurin inhibitors under occlusion for the treatment of atopic eczema in children and, if effective, for how long can they safely be used?

Why this is important
Occlusion increases absorption of a drug but this also increases the systemic effects. Increasing the effectiveness may compromise safety, particularly if a large surface area is involved. Such research would help to ascertain safety and efficacy of occlusion, particularly in the case of the topical calcineurin inhibitors, where there are no clinical data and little clinical experience of such use.

Antihistamines and other antipruritics

What is the clinical effectiveness, cost-effectiveness and safety of using sedating and non-sedating antihistamines in children with atopic eczema in terms of the outcomes itch and night-time sleep disturbance?

Why this is important
Antihistamines are frequently used to reduce itching and as night-time sedation for younger children with atopic eczema, often to allow parents some sleep. In school-age children the non-sedating antihistamines are sometimes used to reduce daytime itch. There are no data to support the use of antihistamines as an effective clinical strategy. However, lack of data does not mean lack of efficacy and some children describe them as helpful in reducing itch and improving sleep. This is a cost issue and important from clinical and patient perspectives.

Treatment for infections associated with atopic eczema

What are the prevalence and patterns of antibiotic resistance in children with atopic eczema and how clinically meaningful are these in terms of clinical management and the emergence of multiresistant bacteria?

Why this is important
Up to 80% of children with atopic eczema are known to harbour *Staphylococcus aureus*, although this may not be clinically apparent. There are data to show that there is an increasing resistance (up to 66% of cultures in some UK regions) to antibiotics such as fusidic acid, which is commonly used as a topical agent to treat infected eczema. It is not clear how important this is in clinical practice and what danger it poses to society as a whole. Much more information is required to determine the pattern and emergence of resistant strains and their relationship to the use of topical antibiotics.

How should bacterially infected atopic eczema in children be defined, how should it be treated and for how long? What are the indications for use of antimicrobial agents in terms of their clinical effectiveness (including palatability), cost-effectiveness and safety?

Why this is important
Bacterial colonisation of atopic eczema in children is common (up to 80% of cases) but not all will develop clinically manifest infection. However, secondary infection is a common cause of flares of eczema and is often unrecognised by healthcare professionals and parents/carers. Unnecessary use of antibiotics is expensive and potentially dangerous (in terms of systemic effects, development of allergy and emergence of multiresistant strains of microorganisms). Information from research is required to enable clear treatment plans to be made about when and for how long to use antimicrobial agents and which agents are the safest and most suitable for different ages of child.

Phototherapy and systemic treatments

How effective, cost-effective and safe is phototherapy in children with severe atopic eczema? How and when should it be used and should it be combined with other topical therapies?

Why this is important
Phototherapy is often used for children with severe atopic eczema but there are few studies reporting on its effectiveness, cost-effectiveness and long-term safety. High-quality RCTs are needed which should include comparisons with different types of phototherapy and in combination with different topical therapies.

How effective, cost-effective and safe are systemic treatment options in children with severe atopic eczema and how and when should they be used? For example: azathioprine, ciclosporin, methotrexate, mycophenolate mofetil, oral prednisolone and the newer biological agents.

Why this is important
Direct comparisons of the effectiveness of the systemic treatment options in children with severe atopic eczema are required, focusing on quality of life and long-term safety. All these treatment strategies are currently unlicensed for use in children under 12 years of age and should be restricted to specialist use.

Complementary therapies

How effective, cost-effective and safe are complementary therapies for the management of atopic eczema in children and how do they compare with conventional Western therapies?

Why this is important
There are almost no data on the effectiveness of complementary treatment for children with atopic eczema, although there are some data to suggest that up to 60% of parents have tried these. High-quality RCTs are needed which should include comparisons with placebo controls and different forms of conventional and complementary medicine, used alone or in combination with each other. This will aid patient and physician choice and answer many unanswered questions. It has potential cost and licensing implications.

Behavioural therapies

Are behavioural and psychological interventions, for example habit reversal techniques, effective in the management of atopic eczema in children and would their use be feasible and cost-effective in clinical practice?

Why this is important
There are data to show that atopic eczema can have a negative psychological effect on children and their family. Adults with atopic eczema admit that they 'habit scratch', which perpetuates the disease and this is often true for children as well. There are also quality of life data to suggest that atopic eczema is worse than having other chronic childhood diseases. However, there are almost no data examining the effects of psychological interventions to treat these effects. Access for psychological help in the NHS is currently very limited and waiting lists are long. Such research would help to utilise scarce resources effectively and assist future service planning.

Chapter 8 Education and adherence to therapy

How effective and cost-effective are different models of educational programmes in the early management of atopic eczema in children, in terms of improving adherence to therapy and patient outcomes such as disease severity and quality of life?

Why this is important
Atopic eczema is a common childhood disease affecting one in five children in the UK. Effective therapy improves quality of life for children with atopic eczema and their parents and carers, and can be provided for over 80% of children with atopic eczema in a primary care setting. It is known that a lack of education about therapy leads to poor adherence, and consequently to treatment failure.

Chapter 9 Monitoring growth

Which factors contribute to growth delay in children with severe atopic eczema, how should they be managed and does this impact on their expected final adult height?

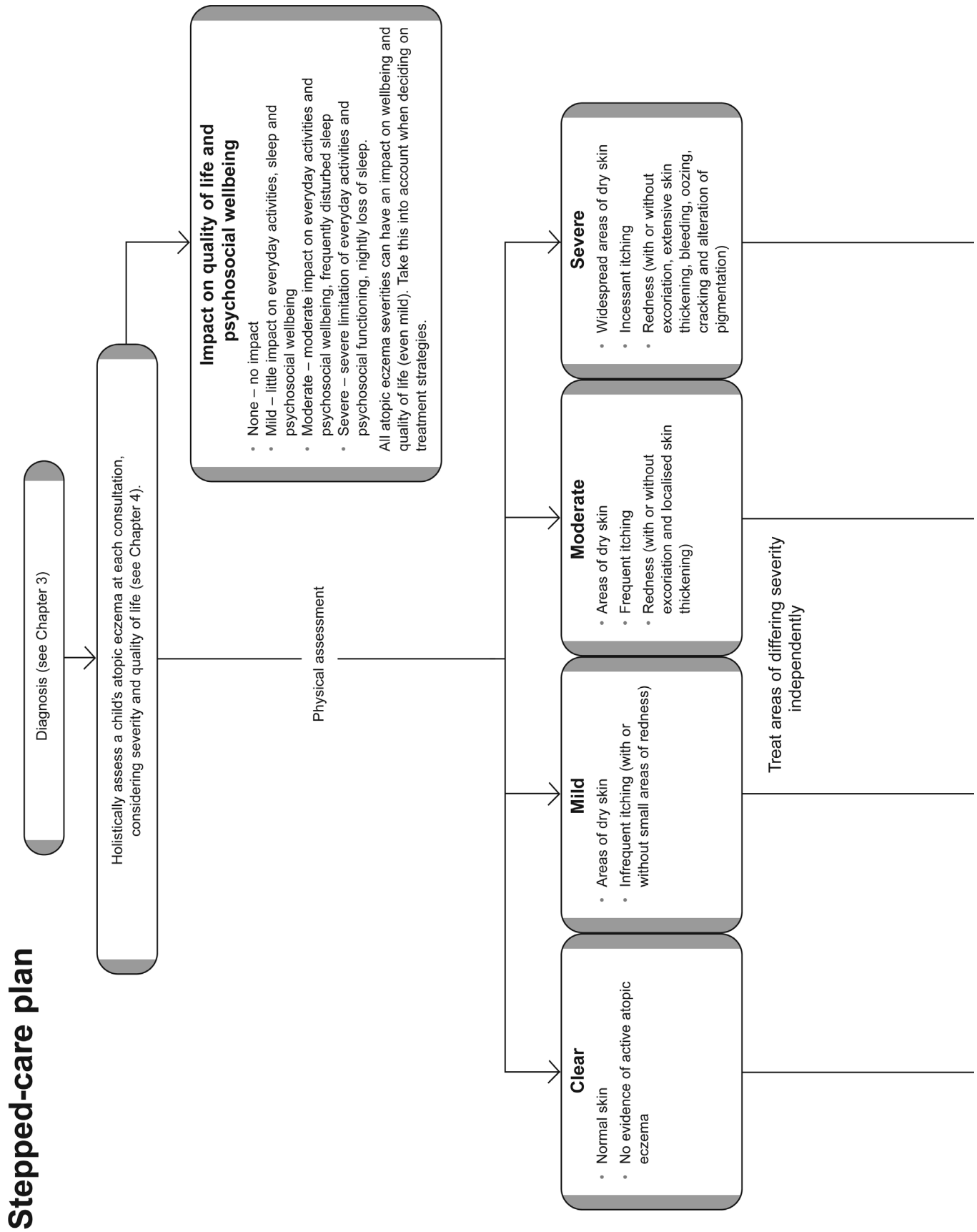
Why this is important
It is known that 10% of children with severe atopic eczema have a corrected height below that expected from centile charts based on the general UK after taking into account their parental heights. However, the causes for this are not fully understood. This study is necessary to understand the causes of growth delay in order to provide the correct management to maximise 'catch up' growth and achieve an adult height appropriate for that child. The study should consider the effects of chronic stress and sleep disturbance on the growth of children with atopic eczema.

What is the impact of food allergy on growth in infants with atopic eczema and how should it be managed?

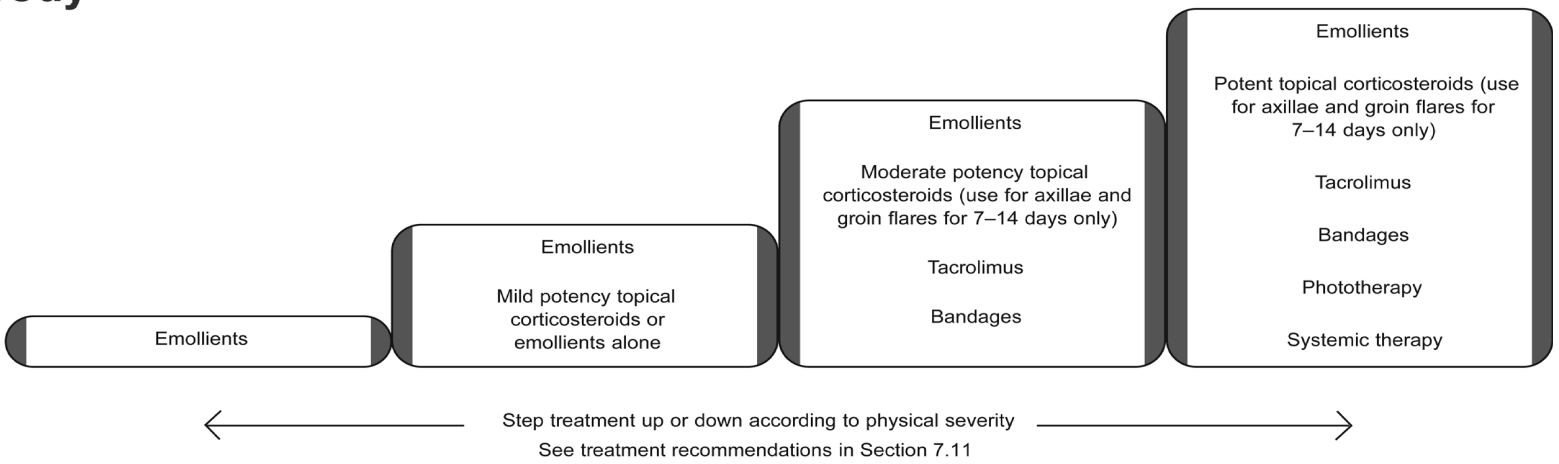
Why this is important
Food allergy should be suspected in infants with atopic eczema and failure to thrive. The percentage of children with eczema who have poor growth because of food allergy is not currently known. Research is required to determine this in order to plan the most effective and cost-effective feeding regimens to manage these children.

2.5 Treatment algorithm

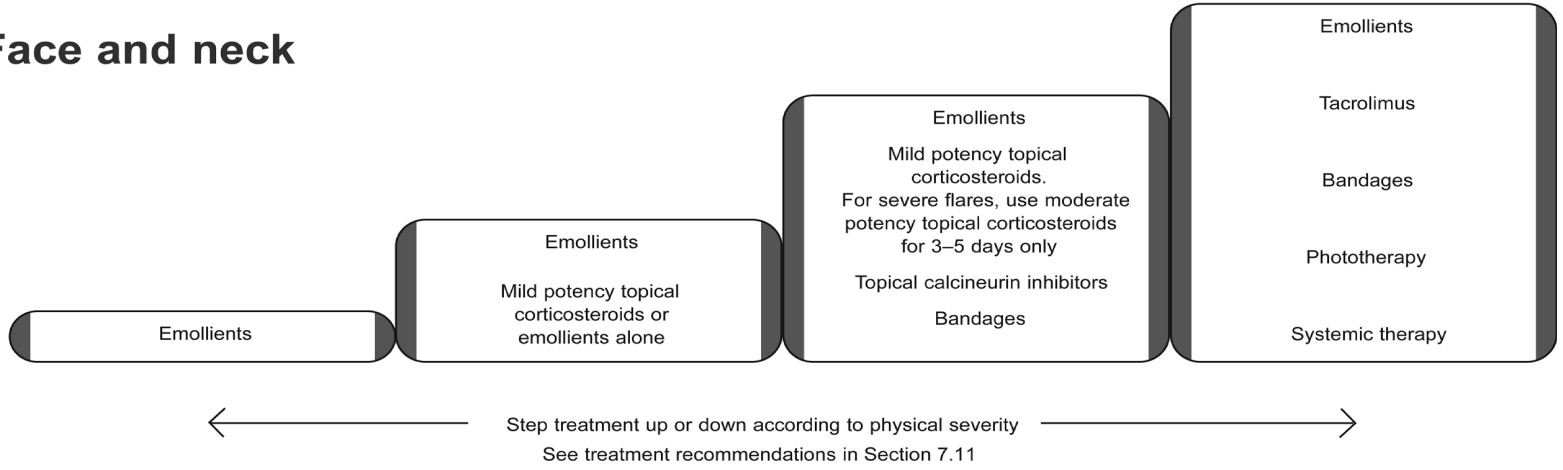
The treatment algorithm overleaf is taken from the NICE Quick Reference Guide version of this guideline (www.nice.org.uk/CG057GQuickRefGuide).


Stepped-care plan
Diagnosis (see Chapter 3)
Holistically assess a child's atopic eczema at each consultation, considering severity and quality of life (see Chapter 4).
Impact on quality of life and psychosocial wellbeing
None – no impact
Mild – little impact on everyday activities, sleep and psychosocial wellbeing
Moderate – moderate impact on everyday activities and psychosocial wellbeing, frequently disturbed sleep
Severe – severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep.
All atopic eczema severities can have an impact on wellbeing and quality of life (even mild). Take this into account when deciding on treatment strategies.
Physical assessment
Clear
Normal skin
No evidence of active atopic eczema
Mild
Areas of dry skin
Infrequent itching (with or without small areas of redness)
Moderate
Areas of dry skin
Frequent itching
Redness (with or without excoriation and localised skin thickening)
Severe
Widespread areas of dry skin
Incessant itching
Redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation)
Treat areas of differing severity independently

Body



Face and neck



3 Diagnosis

The diagnosis of atopic eczema relies on the assessment of clinical features because there is no laboratory marker or definitive test that can be used to diagnose the condition. Diagnostic criteria for atopic eczema were originally developed in an attempt to standardise the type of patient enrolled in research studies. The first such criteria, which were published in 1980 by Hanifin and Rajka, categorised signs and symptoms into four major criteria and more than 20 minor criteria; a diagnosis of atopic eczema required the presence of at least three criteria from both categories.[25] The criteria were agreed by consensus, and their validity and repeatability in relation to a clinician's diagnosis is unknown.[26,27]

In 1994 a UK Working Party published a minimum list of criteria for atopic dermatitis, which were derived from the Hanifin and Rajka criteria.[27-29]

Studies considered in this chapter

In this chapter validation studies for diagnostic criteria are considered. Validation studies for the UK Working Party's diagnostic criteria were identified. Although other diagnostic criteria for atopic eczema have been described, such as the Lillehammer criteria and questionnaires used for epidemiological studies, no validation studies were identified for these criteria.

No evidence comparing outcomes for children diagnosed with atopic eczema using different criteria was identified. Studies comparing epidemiological data obtained by using different diagnostic criteria are not relevant to this section.

Overview of available evidence

The UK Working Party criteria were developed by comparing observations made by two observers (dermatology registrars or senior registrars) using 31 of the Hanifin and Rajka criteria, with the definitive diagnosis of atopic eczema being made by a physician with an interest in dermatology.[27] The observers were unaware of the true purpose of the study. Sixteen physicians were involved in the study, 13 of whom had a special interest in atopic eczema, including six paediatric dermatologists. The study population consisted of consecutive new cases of 'typical mild to moderate atopic eczema' (patients aged 6 months to 50 years) and two control groups (patients with an inflammatory skin disorder other than atopic eczema attending the clinic, and patients from the community with no overt skin disease; total n = 224, 120 cases and 104 controls). Overall, 53% of the cases were aged under 10 years; 35% of the total study population were aged under 10 years and 46% were aged under 16 years. Cases were significantly younger than controls ($P < 0.01$). The study population was predominantly white (82%), and the ethnic origin of the remaining individuals was the Indian subcontinent (5%), Afro-Caribbean (9%), oriental (3%), and 'other' (1%). Non-white people were significantly under-represented in the control group ($P = 0.01$).[27] [EL = 2+/DS II]

The sensitivity and specificity of each criterion was calculated using the physician's diagnosis as the gold standard and the observer's diagnosis as the 'test'. Regression techniques were used to derive the minimum set of criteria that best discriminated between cases of atopic eczema and controls; these techniques included the chi-squared test, consideration of the intra-observer reliability, and the sensitivity and specificity values. Six criteria were found to provide good separation of atopic eczema cases from controls, namely:[27]

- history of flexural dermatitis
- history of dry skin
- onset under the age of 2 years
- history of a pruritic skin condition ('presence of an itchy rash')
- personal history of asthma
- visible flexural dermatitis.

The investigators also explored whether the six criteria were influenced by ethnic group. They reported that there was no evidence of a difference, but no data were presented.

The proposed composite criteria (itchy skin as a major criterion, with three or more of the other five criteria) were validated in studies undertaken in outpatient settings.[28] [EL = DS Ib] The populations considered were dermatology outpatients (27% of whom were children aged 10 years or under) and paediatric outpatients. While the dermatology outpatients study included some data for children within the age group of interest to this guideline, no demographic data were provided and therefore that part of the study is not considered further.

Some criteria 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 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 atopic 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 under 4 years, and 'history of flexural dermatitis' included dermatitis on the cheeks in children under 10 years.[28]

The paediatric outpatient study, conducted in the London area, included 114 children aged up to 16 years (39 children with atopic eczema and 75 controls). The median ages of cases and controls (interquartile range) were 5 years (2–10 years) and 6 years (3–9 years), respectively. Overall, 51% were female, 51% were white, 27% were Afro-Caribbean, 11% were from the Indian subcontinent, and 11% were Chinese, Middle Eastern or of mixed race. Control groups had conditions such as other inflammatory dermatoses or infections.[28]

The conclusion was that optimal discrimination was given by itch plus three or more other criteria. The sensitivity of these diagnostic criteria was 85% (95% confidence interval (CI) 60% to 94%) and the specificity was 96% (95% CI 89% to 99%).[28] This indicates that 85% of children diagnosed with atopic eczema by a dermatologist were also diagnosed with atopic eczema using the composite criteria. The specificity value indicates that 96% of those who were not diagnosed with atopic eczema by a dermatologist were also not diagnosed with the condition using the composite criteria. When the specificity is very high, the rate of false positives is conversely low. Therefore, a positive test result implies a correct diagnosis. The sensitivity and specificity of the composite criteria were considered to be similar in the Afro-Caribbean subgroup to those in the total population.[28]

Validation studies of the UK Working Party's diagnostic criteria for atopic dermatitis have also been undertaken in community populations (schoolchildren in London,[30] Romania,[31] and South Africa,[32] and in Scottish infants aged 1 year[33]). There was one study in a clinical setting in India.[34] Other validation studies identified have included both children and adults, but do not report data separately for children and therefore are not considered further.[35,36]

The validation studies tended to focus on the predictive value of individual criteria and of composite criteria (itch plus a number of other criteria). In the South African study,[32] questionnaires including all six questions were administered by fieldworkers. [EL = DS III] In the other studies, parents, children or schoolteachers completed questionnaires that included five of the six UK Working Party criteria. A nurse independently assessed whether the sixth criterion (visible flexural dermatitis) was present. The diagnostic accuracy of each criterion was then compared with the diagnosis made by a dermatologist (regarded as the gold standard diagnosis).[30,31] [EL = DS II]

The studies in schoolchildren in London (n = 695) and Romania (n = 1114) were identical in design. The London children were aged 3–11 years and included a range of ethnic groups (43% white, 8% Indian subcontinent, 32% black, 15% mixed, 2% other).[30] The Romanian children were aged 6–12 years and were predominantly white Romanian (98%), the remainder being Gypsy (1%), mixed race (1%), or 'other' (0.1%).[31] The prevalence of atopic eczema in the London and Romanian school children was 8.5% and 2.4%, respectively.

From these studies, the composite criterion of itch plus three or more other criteria was regarded as providing the best diagnostic information (that is, providing the best separation of cases from non-cases). Compared with a dermatologist's diagnosis, the composite criterion provided the following diagnostic accuracy statistics:

- sensitivity 70%, specificity 93%, PPV 47%, NPV 97% in London schoolchildren[30]
- sensitivity 74%, specificity 99%, PPV 63%, NPV 99% in Romanian schoolchildren.[31]

The results show that the level of agreement for a negative diagnosis is high. The relatively low PPVs reflect the low prevalence of atopic eczema in the study populations. It is expected that in clinical situations where the diagnostic criteria are to be used that the prevalence would be much higher and therefore the PPV would also increase.

The validity of the criteria in certain subgroups (including groups based on age and ethnicity) was also explored, although results were given only for those aged under 4 years and according to severity. The study in London schoolchildren also considered the retest reliability of the questionnaire in 73 cases. Kappa scores were above 0.85, indicating a good level of agreement between first and second questionnaires.[30]

The South African study comprised Xhosa-speaking schoolchildren (*n* = 3067, age 3–11 years) from urban, peri-urban and rural areas.[32] The original questionnaire was translated into Xhosa, validated in a pilot study and administered by a bilingual interviewer. For the UK diagnostic criteria, specificity was high (97.9%, 95% CI 97.3% to 98.4%). Sensitivity of 43.7% (95% CI 26.3% to 62.3%) means that over half of the children diagnosed with atopic eczema by a dermatologist were misclassified by the diagnostic criteria. The single criterion of visible flexural eczema had sensitivity of 81.2% (95% CI 63.5% to 92.7%) and specificity of 99.0% (95% CI 98.6% to 99.3%), implying that this criterion alone has the ability to distinguish between cases and non-cases in this population. The prevalence of atopic eczema in this group was 1.0% (95% CI 0.6% to 1.4%).

The validation study of infants in Scotland considered level of agreement (percentage and kappa scores) between a parent's and a nurse's diagnosis of atopic eczema in cases and controls using the UK Working Party's criteria (*n* = 108).[33] [EL = 2+] Parents completed a postal questionnaire listing the criteria. The percentage agreement for five of the six criteria ranged from 88% to 97% (kappa scores 0.75 to 0.94). (The criterion 'onset in age under 2 years' is irrelevant in this study because the entire study population was aged under 2 years). The levels of agreement between mothers and nurses for composite criteria were 96% for itch plus three or more other criteria, and 94% for itch plus all UK criteria.[33]

The study in India[34] (*n* = 149, age 2 months to 14 years) compared the Hanifin and Rajka criteria and the UK Working Party diagnostic criteria with each other and with clinical diagnosis by a dermatologist. A questionnaire was designed that included all of the features of both sets of criteria. This questionnaire was administered to 101 children with atopic dermatitis and 48 children with other skin conditions. It was not stated whether the clinical diagnosis was known by the interviewers. The UK Working Party diagnostic criteria were found to have high sensitivity (86%) and specificity (96%). [EL = DS III]

Evidence statement for diagnosis

A range of diagnostic criteria for atopic eczema in children have been described in the literature, but only the UK Working Party criteria have been assessed adequately for validity and repeatability. The use of composite criteria of itch plus another three or more of the five criteria is considered to provide optimal separation of children with or without the condition. In validation studies in European children aged 1–12 years, the UK Working Party criteria provided a valid tool for diagnosing atopic eczema in community settings. [EL = 2+/DS II] In the South African study, the composite criteria did not distinguish cases from non-cases adequately, although the single criterion of visible flexural eczema did. [EL = DS III] The high specificity in all of the validation studies means that the false positive rate is low and therefore a diagnosis of atopic eczema according to the UK working party criteria should be believed.

Cost-effectiveness

Published evidence relating to the cost-effectiveness of diagnostic criteria was not sought because the use of healthcare resources was not the focus of the clinical question.

From evidence to recommendations

In the absence of outcome data for any diagnostic method, the GDG consensus view was that the UK Working Party's diagnostic criteria would help clinicians with little knowledge or experience

of dermatology to diagnose atopic eczema in children. Using the diagnostic criteria may also optimise the use of consultation time.

It is the GDG's view that the proposed diagnostic criteria apply to all ethnic groups, although it is recognised that there are differences in the pattern of atopic eczema among different ethnic groups. For example, in children of black African, black Caribbean or Asian origin atopic eczema may present on extensor surfaces as well as on flexures, and is more likely to produce lichenification (thickening of the skin), lumpy or papular skin (papular or follicular eczema) and a change in pigmentation. [EL = 4]

The potential impact of using the proposed criteria on consultation time for diagnosis was considered by the GDG. The likelihood is that using diagnostic criteria such as these would focus history taking and physical examination compared with not using formal criteria, and therefore would not increase consultation time or cost.

The GDG also believes that taking a thorough history that includes questions about potential trigger factors and the presence of other atopic diseases is an important step in the management of atopic eczema in children.

Recommendations for diagnosis

To aid management of atopic eczema in children, healthcare professionals should take detailed clinical and drug histories that include questions about:

- time of onset, pattern and severity of the atopic eczema
- response to previous and current treatments
- possible trigger factors (irritant and allergic)
- the impact of the atopic eczema on children and their parents or carers
- dietary history including any dietary manipulation
- growth and development
- personal and family history of atopic diseases.

Atopic eczema should be diagnosed when a child has an itchy skin condition plus three or more of the following:

- visible flexural dermatitis involving the skin creases, such as the bends of the elbows or behind the knees (or visible dermatitis on the cheeks and/or extensor areas in children aged 18 months or under)
- personal history of flexural dermatitis (or dermatitis on the cheeks and/or extensor areas in children aged 18 months or under)
- personal history of dry skin in the last 12 months
- personal history of asthma or allergic rhinitis (or history of atopic disease in a first-degree relative of children aged under 4 years)
- onset of signs and symptoms under the age of 2 years (this criterion should not be used in children aged under 4 years).

Healthcare professionals should be aware that in Asian, black Caribbean and black African children, atopic eczema can affect the extensor surfaces rather than the flexures, and discoid (circular) or follicular (around hair follicles) patterns may be more common.

Research recommendations for diagnosis

What is the validity of currently used diagnostic criteria for atopic eczema when used in different ethnic groups?

Why this is important
Atopic eczema has a different clinical presentation in some ethnic groups with greater lichenification and papulation and a predilection for extensor rather than flexural areas. The UK diagnostic criteria have not been tested extensively in non-white ethnic groups in the UK.

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

4.1 Assessment of severity

There is no gold standard serological or laboratory test for assessing the severity of atopic eczema. Measurements have traditionally been based on the assessment of one or more of the following disease parameters:[37,38]

- clinical signs (visible skin changes) associated with disease activity
- disease extent (the area of skin affected by atopic eczema)
- patient symptoms (such as itching and sleep disturbance)
- global (overall) assessments of disease activity by the physician, child or parent (for example, mild, moderate or severe)
- the quantities or strengths of treatment required
- the impact of the disease on the quality of life of the child and their family.

A number of severity scales (hereafter referred to as named instruments) can be used to measure these parameters, either grading patients into a disease severity category (for example, mild, moderate or severe) or providing a numerical disease severity score. Scores from the measurement of a number of different items (such as individual clinical signs) or disease parameters can also be combined to form a severity index.[39,40]

Studies considered in this section

No studies were identified that addressed the clinical utility of named instruments for measuring severity of atopic eczema in routine clinical practice. Therefore, studies that were designed to validate measurement instruments were considered in this section. Various studies evaluated the validity, reliability, responsiveness (sensitivity to change) and acceptability of instruments (see Table 4.1 for definitions of these terms).

Studies that used named instruments to evaluate the effects of interventions for atopic eczema are described in Chapter 7. It is recognised that such studies provide some validation of the instruments although the studies were not designed for this purpose.

A systematic review (end search date April 1999)[39] considered available validity data for named instruments for measuring the severity of atopic eczema. A further systematic review (end search date December 2001)[40] aimed to determine which measurement instruments had been used in clinical trials. Studies included in the systematic reviews that are relevant to the population for which this guideline is intended are considered here together with studies published since the reviews.

Overview of available evidence for named measurement instruments

Thirteen named measurement instruments have been evaluated for assessing the severity of atopic eczema in children, as summarised in Table 4.2. Some of the instruments measure severity at a

Table 4.1 Properties of severity measurement instruments for atopic eczema; modified with permission from Charman and Williams[39], *Archives of Dermatology* 2000;136(6):763–9, Copyright © 2000, American Medical Association, all rights reserved

Property	Definition
Validity	Does the instrument measure what it is intended to measure?
Content validity	Does the instrument appear to be assessing all the relevant content or domains, based on judgement by one or more experts?
Construct validity	Does the instrument agree with other related variables and measures of the same construct with which, in theory, it ought to agree (e.g. topical corticosteroid requirements, time off school, or visits to a physician)?
Criterion validity	Does the instrument correlate with some other measure of the disease, ideally a 'gold standard' that has been used and accepted in the field?[a]
Reliability	Does the instrument measure what it is intended to measure in a reproducible fashion?
Inter-observer reliability	Do measurements made by two or more observers produce the same or similar results?
Intra-observer reliability	Do measurements made by the same observer on two or more occasions produce the same or similar results?
Internal consistency	Do the scores from different items on the instrument correlate with each other and with the total score (i.e. are all items in the instrument measuring the same attribute)?
Responsiveness	Is the instrument sensitive enough to detect clinically relevant changes in disease severity?
Acceptability	Is the instrument simple to administer for both the patient and assessor?

[a] Measurement of criterion validity ideally involves comparison with a 'gold standard' measure. As there is no accepted gold standard for measuring the severity of atopic eczema most studies used at least one other instrument as a comparison of the criterion validity of the instrument under evaluation.

single point in time (when administered), whereas others measure severity over a period of time (such as the previous week).[39,40] [EL = 3]

No studies were identified that evaluated the validity, reliability, sensitivity to change or acceptability of the Skin Intensity Score (SIS), Atopic Dermatitis Severity Index (ADSI), Atopic Dermatitis Area and Severity Index (ADASI), or Rajka and Langeland's scoring system in children.

The validation data for the 13 named instruments listed in Table 4.2 are described below.

Atopic Dermatitis Assessment Measure (ADAM)
Two validation studies in children were identified for the Atopic Dermatitis Assessment Measure (ADAM).[41,42] [EL = 3] The instrument was used by the treating doctor and criterion validity was tested against a physician's global rating of severity ('trivial', mild, moderate or severe) and showed 'marginal' agreement (kappa score 0.4, $P < 0.05$), with better agreement for mild than severe atopic eczema ($n = 171$).[42] Reliability testing showed variable inter-observer agreement for individual elements of the score with none having a kappa score of 0.7, which was the level of agreement set *a priori* to be statistically significant ($n = 51$).[41] No studies reporting responsiveness or acceptability of the ADAM instrument in children were identified.

Basic Clinical Scoring System (BCSS)
Some data for the validity and inter-observer reliability of the Basic Clinical Scoring System (BCSS) were reported in one study that compared the findings of three instruments (BCSS, the Scoring Atopic Dermatitis (SCORAD) index and Costa's Simple Scoring System (Costa's SSS)) in children and adults ($n = 82$).[57] [EL = 3] In this study all questionnaires were used by one physician trained in their use. Agreement for BCSS versus SCORAD and versus Costa's SSS was found to be poor (kappa scores of 0.38 and 0.21, respectively). Inter-observer agreement, between two physicians, for BCSS was high (kappa score 0.9). Responsiveness to change was shown in one study.[43] No studies were identified that considered acceptability of the BCSS instrument in children.

Table 4.2 Summary of named instruments for measuring severity of atopic eczema in children

Instrument	Description
ADAM[41,42]	Atopic Dermatitis Assessment Measure: assessment of pruritus on a scale of 0–3; six body areas for scale/dryness, lichenification, erythema and excoriations on a scale of 0–3; four body areas assessed for the presence or absence of eczema; plus a global rating of severity (on a scale of 0–3)
BCSS[43]	Basic Clinical Scoring System: assessment for the presence or absence of disease in five body sites (maximum score 5)
Costa's SSS[44]	Costa's Simple Scoring System: assesses 10 severity criteria (on a scale of 0–7), and the extent of atopic eczema in 10 topographic sites (on a scale of 0–3), giving a maximum score of 100.
EASI[45] (and SA-EASI[46])	Eczema Area and Severity Index: assessment of disease extent in four defined body regions (on a scale of 0–6) combined with an assessment of erythema, infiltration/papulation, excoriation and lichenification (on a scale of 0–3). A formula is used to calculate the total score by multiplying the sum of the body area scores by the clinical sign scores (maximum score 72). The Self-Administered Eczema Area and Severity Index is a measurement instrument for caregivers based on an assessment of disease extent (shading affected areas on a line drawing silhouette), and five visual analogue scales for redness, thickness, dryness, number of scratches and itchiness.
IGA[47]	Investigator's Global Assessment: overall severity of atopic eczema on a six-point scale (0 = totally clear to 5 = very severe).
NESS[48] (and SA-NESS[49])	Nottingham Eczema Severity Score: measures clinical course and sleep disturbance over the previous 12 months (each on a five-point scale), and the extent of atopic eczema using a tick box chart (also on a five-point scale), giving a maximum score of 15. It is proposed that scores of 3–8, 9–11 and 12–15 represent mild, moderate and severe disease, respectively. A Self-Administered NESS (SA-NESS) questionnaire has also been described.[49]
OSAAD[50]	Objective Severity Assessment of Atopic Dermatitis: a score calculated according to a formula based on measurements of cutaneous transepidermal water loss and hydration, multiplied by computer-estimated body surface area measurements.
POEM[51]	Patient-Oriented Eczema Measure: a self-assessed questionnaire that assesses the frequency of itch, sleep disturbance, bleeding, weeping/oozing, cracking, flaking and dryness of skin (on a scale of 0–4) over the previous week, giving a maximum score of 28. It is designed to be completed by the child or parent, depending on the age and understanding of the child.
SASSAD[52]	Six Area, Six Sign Atopic Dermatitis index: assessment of six clinical features of disease intensity (erythema, exudation, excoriation, dryness, cracking and lichenification) at six body sites on a scale of 0–3 (maximum score 108).
SCORAD[53,54]	Scoring Atopic Dermatitis: a composite index comprising an assessment of six clinical features of disease intensity on a single representative site (on a scale of 0–3) combined with measurement of disease extent using the 'rule of nines'[a] (0–100) and an assessment of itch and sleep loss over the last 3 days and nights (visual analogue scales of 0–10). A formula is then used to calculate the total score based on the addition of weighted scores for disease extent, disease intensity (clinical signs) and patient symptoms, giving a maximum score of 103. The objective components of the SCORAD index (clinical signs and disease extent, total score 83) are used to classify atopic eczema severity as mild (< 15), moderate (15–40) or severe (> 40). Objective Scoring of Atopic Dermatitis: adjusted SCORAD index excluding the subjective measures of itch and sleep loss (maximum score 83).
Skin Detectives Questionnaire[56]	A self-assessment tool based on the SCORAD index.
TIS[55]	Three Item Severity score: a simplified version of the objective SCORAD comprising an assessment of erythema, oedema/papulation and excoriation. Each clinical sign is assessed on a representative body site as in the SCORAD index on a scale of 0–3, giving a maximum score of 9.

* In the rule of nines, various areas of the body are scored as follows: trunk (front and back) 36%, legs 36%, arms 18%, head and neck 9%; hands and genitalia 1%.

Costa's Simple Scoring System (Costa's SSS)
Some data for the validity and inter-observer reliability of Costa's SSS were reported in the study described above that compared the findings of three instruments (Costa's SSS, BCSS and SCORAD) in children and adults (n = 82).[57] [EL = 3] As noted above, agreement between the three instruments was poor (kappa scores of 0.38 for SSS versus SCORAD and 0.21 for SSS versus BCSS). Significant inter-observer variation was reported in the assessment of excoriations and 'scales'.[57] [EL = 3] No data were found regarding the sensitivity to change in children with atopic eczema.[58]

Eczema Area and Severity Index (EASI)
Validity and/or reliability of the Eczema Area and Severity Index (EASI) have been reported in two studies involving children.[47,59] Criterion and construct validity were shown in one study where good correlation was seen between EASI scores and patient assessment scores, Investigator's Global Assessment (IGA) scores and assessments of pruritus (Kendall's correlation coefficient 0.581–0.753 at 6 weeks to 6 months, Spearman's correlation coefficient 0.727–0.877, n = 1550).[47] The correlation between EASI scores and quality of life scores (Parents' Index of Quality of Life (PIQoL)) was poor (Kendall's correlation coefficient 0.263–0.340, Spearman's correlation coefficient 0.37–0.49). Internal consistency and responsiveness were also shown in this study, with good correlation between three items of the scale (erythema, infiltration and/or papulation), whereas lichenification correlated less well with the other items.[47] Reliability testing showed 'fair to good' inter-observer and intra-observer agreement (defined as correlation coefficients of 0.4–0.75), n = 10 children; 15 observers).[59] Inter-observer variability was greater for induration/papulation than the other three signs.[59] [EL = 3] No data on acceptability were identified.

Self-Administered Eczema Area and Severity Index (SA-EASI)
One study considered the validity of the Self-Administered Eczema Area and Severity Index (SA-EASI) in children by comparing total scores with those obtained using the EASI instrument (n = 47).[46] [EL = 3] Good correlation between overall scores was shown, but agreement between visual analogue scale intensity ratings using SA-EASI (redness, thickness, and scratches) and corresponding individual components of EASI (erythema, papulation/induration/oedema, and excoriation, respectively) was poor.[46] No studies considering the reliability, responsiveness or acceptability of SA-EASI were identified. Another study found 'poor to moderate' correlation at one time point (no further details were reported) and no correlation at another time point between SA-EASI and parents' perception of severity. The study reported a correlation between SA-EASI and the Atopic Dermatitis Family Impact Scale (ADFIS), which was based on the Dermatitis Family Impact (DFI) scale (see Section 4.3).[60]

Investigator's Global Assessment (IGA)
As described above, the IGA has shown good correlation with the EASI instrument.[47] [EL = 3] No studies were identified that investigated the reliability of the IGA. Responsiveness has been shown in several clinical trials (see Chapter 7). No data on acceptability were identified.

Nottingham Eczema Severity Score (NESS)
In the original description of the Nottingham Eczema Severity Score (NESS), validity was tested by examining agreement between the NESS and global assessments of disease severity made by a dermatologist and parents (mild, moderate or severe; n = 290).[48] There was exact agreement between NESS and a dermatologist's global severity assessment 88% of the time, and exact agreement between NESS and a parental global severity assessment 75% of the time. Construct validity testing showed a trend towards use of higher potency topical corticosteroids with increasing values of NESS. The correlation between NESS and the Children's Life Quality Index (CLQI; a, generic, proxy measure of quality of life in the previous 3 months) was 'poor'. The NESS questionnaire was 'easily completed in a few minutes'.[48] [EL = 3] Chinese translations of the NESS have shown correlation with the SCORAD index.[49,61] No studies considering the reliability or responsiveness of NESS in children were identified.

A Chinese translation of NESS has been adapted into a self-assessment severity score (SA-NESS) in which children or their parents (rather than a physician) assess disease extent using a tick box chart. Weighted kappa scores for the level of agreement between physician's and child's/parent's grading ranged from 0.74 to 0.89, indicating good agreement.[49] [EL = 3]

Objective Severity Assessment of Atopic Dermatitis (OSAAD)
The Objective Severity Assessment of Atopic Dermatitis (OSAAD) score showed good correlation (Spearman's correlation coefficient 0.63) with the SCORAD index in one study involving children (*n* = 38).[50] [EL = 3] No studies were identified that investigated the reliability, responsiveness or acceptability of the OSAAD score in children.

Patient-Oriented Eczema Measure (POEM)
The symptoms included in the Patient-Oriented Eczema Measure (POEM) instrument were derived from interviews with children and adults, thereby establishing content validity of the measure (*n* = 435).[51] [EL = 3] Criterion validity is supported by good correlation with child/parental global assessments of disease severity and overall 'bother' related to the atopic eczema. Good correlation was also shown between the POEM and the Children's Dermatology Life Quality Index (CDLQI). Internal consistency was high, confirming that the various components of the score were measuring different aspects of the same disease. Good test–retest reliability was seen in 50 patients who completed POEM twice (difference between the scores 0.04).[51] [EL = 3] The questionnaire takes 1–2 minutes to complete. POEM has been used in intervention studies where it has shown sensitivity to change. No information regarding acceptability of the instrument in children was identified. The POEM questionnaire is available at www.nottingham.ac.uk/dermatology/POEM.htm.

Six Area, Six Sign Atopic Dermatitis (SASSAD) index
No studies were identified that considered validity of the Six Area, Six Sign Atopic Dermatitis (SASSAD) index in children. The inter- and intra-observer reliability of the SASSAD index was evaluated in one small study (*n* = 6, including three children).[62] [EL = 3] Good overall inter-observer agreement was found for total scores (intraclass correlation coefficient 0.7), but agreement for individual components of the score was poor to moderate. The maximum intra-observer variation was 8 out of a potential score of 108.[62] Sensitivity to change in children has been shown.[52,63,64] The questionnaire takes 2–10 minutes to complete.[52]

Earlier versions of the SASSAD index have been described (Leicester index[65,66] and Total Body Severity Assessment[67]), but they have not been evaluated in children and are not discussed further.

Scoring Atopic Dermatitis (SCORAD) index
The SCORAD index has undergone testing for validity, reliability, responsiveness and acceptability.[39,40] It has been shown to be correlated with transepidermal water loss, skin hydration and stratum corneum integrity,[68] providing evidence for construct validity of the index. [EL = 3]

Criterion validity of the SCORAD index is supported by correlation with global assessments of disease severity[39] as well as with other measurement instruments such as NESS[61] and OSAAD,[50] and with nocturnal activity in children.[69] [EL = 3] As noted above, agreement between the SCORAD index, BCSS and Costa's SSS was found to be poor in a study involving children and adults (*n* = 82).[57]

Internal consistency has been demonstrated, with individual items contributing to the index being positively correlated with each other and the total score.[53,70] Correlations between objective items (extent and intensity) and subjective items (sleep loss and pruritus) were weak,[71] but this is to be expected since the objective and subjective items were designed to measure different attributes. [EL = 3]

The inter-observer reliability of SCORAD has been investigated in five studies and reported to show significant variation in one or more elements in each study. In the development of the SCORAD index, significant inter-observer variation was seen in the parameters oedema/papulation, oozing and lichenification (*n* = 88).[53] [EL = 3] Further validation of the index showed variation in the elements lichenification and disease extent (*n* = 19),[54] lichenification and excoriation,[72] oedema/papulation, erythema and excoriations,[57] and lichenification, excoriation and disease extent.[73] One of these studies, which was epidemiological in design, reported that the inter-observer variation in lichenification and excoriation led to a significant variability in overall intensity score and total SCORAD score.[72] In one study it was noted that inter-observer reliability was better in

trained dermatologists than non-dermatologists.[73] Good intra-observer reliability was shown in one study using photographic slides of skin affected by atopic eczema (*n* = 10).[53] [EL = 3]

The SCORAD index is the most widely used atopic eczema measurement instrument in clinical research.[39,40] The index has shown sensitivity to small changes in disease severity in clinical trials.[40] After training, the SCORAD index takes 5–10 minutes to complete.[53,72,73] A website is available for training purposes (adserver.sante.univ-nantes.fr).

The objective SCORAD index has shown correlation with measures of quality of life (DFI and CDLQI).[74,75] [EL = 3]

As noted above, one study found significant correlations between nocturnal activity and both the SCORAD and objective SCORAD instruments.[69] [EL = 3]

Skin Detectives Questionnaire
The Skin Detectives Questionnaire is a self-assessment tool based on the SCORAD index. However, in the one publication identified for this instrument, the correlation was 'not high' between patients' and experts' assessments of the severity of dryness in non-inflamed areas, redness in inflamed areas, visible 'knotty swellings' (a term not explained in the original publication) or small blisters, visible weeping or scabbing, traces of scratching and deep creases (*n* = 22).[56] [EL = 3] No studies were found that tested the internal consistency, reliability, responsiveness, or acceptability of the Skin Detectives Questionnaire.

Three Item Severity (TIS) score
A high correlation between Three Item Severity (TIS) and SCORAD scores has been shown,[55] which is to be expected because the TIS is a simplified version of the objective SCORAD index covering erythema, oedema/papulation and excoriation. Content validity of the TIS was evaluated in one study which found that, from the patient's perspective, the measurement of the three clinical signs involved in the TIS score provided as much information about disease severity as the more complex objective SCORAD index.[76] [EL = 3]

Total TIS scores have shown 'fair' inter-observer reliability.[55] [EL = 3] Reliability data for the three clinical signs have also been reported during validation of the SCORAD index, with oedema/papulation showing most variation between observers.[39,53-55] The three clinical signs have shown sensitivity to change in clinical trials using the SCORAD index.

Other methods of assessing severity

In addition to the measurement instruments described above, a wide range of other measures have been used for assessing the severity of atopic eczema.[40] These include individual components of named measurement instruments and unvalidated combinations of parameters found in named measurement instruments.

Combinations of clinical signs
At least 40 untested combinations of clinical signs (other than those used in the named scoring systems described above) have been used to measure the severity of atopic eczema in clinical trials. Over 30 different clinical signs have been measured using a wide variety of different scales ranging from 0–2 to 0–100.[40]

Patient symptoms
Itch and sleep disturbance were the most commonly measured symptoms, although unvalidated symptoms such as burning, swelling and pain have also been used as measures of disease severity in clinical trials.[40] A variety of different scales ranging from 0–3 to 0–14, including visual analogue scales, have been described for assessing patient symptoms.[40]

Body surface area involvement
Estimates of disease extent are commonly used as a measure of the severity of atopic eczema. At least 20 different methods of estimating body surface area involvement have been identified.[40] [EL = 3] The ill-defined appearance of atopic eczema and complex three-dimensional shape of the human body make accurate percentage disease extent measurements difficult. Inter-observer

reliability of disease extent measurements has been shown to be very poor.[77] [EL = 3] A computer software package designed to assist in disease extent measurements has been described, although the study used artificial painting of skin lesions to improve demarcation, and the validity of this method in the clinical setting is unknown.[78] [EL = 3] One study showed that the relationship between disease extent and patient-rated disease severity was nonlinear, illustrating the fact that small areas of disease on functionally or cosmetically important sites (such as the face, hands or feet) may be classified as severe disease.[76] This study also showed that from the patient's perspective the measurement of three clinical signs (as in the TIS score) reflected disease severity more closely than the measurement of disease extent.

Global scales

A number of unnamed patient- or physician-assessed global scales of the severity of atopic eczema have been identified, with four-point scales being the most widely used (absent, mild, moderate or severe).[40]

Measurements of treatments required

Topical corticosteroid requirements are often recorded in clinical practice and occasionally measured in research,[40] although confounding factors such as adherence to therapy and corticosteroid phobia mean that these measurements do not always provide an accurate reflection of disease severity. One study examined the use of measurements of time spent on treatment as a crude marker of disease severity, but social factors and memory recall were noted to have a significant influence on the scores.[79] [EL = 3]

Measuring severity of atopic eczema in different racial groups

One study using the SCORAD index demonstrated that erythema is difficult to measure accurately in black skin and may lead to underestimates of disease severity in certain racial groups.[80] [EL = 3]

4.2 Assessment of psychological and psychosocial wellbeing

Psychological factors are an important aspect of atopic eczema.[81] Studies have tended to focus on adults, but there is also evidence that atopic eczema causes considerable distress for children and their parents.[82] Preschool children with atopic eczema have higher rates of behavioural difficulties and show greater fearfulness and dependency on their parents than unaffected children.[83] For schoolchildren, problems include time away from school, impaired performance because of sleep deprivation, social restrictions, teasing and bullying.[81] Psychological problems have been found to be twice those of normal schoolchildren among children attending outpatient dermatology clinics with moderate or severe eczema.[81]

Atopic eczema can be associated with poor self-image and lack of self-confidence that can impair social development.[81] It has been shown that children with atopic eczema may be more difficult to parent than unaffected children, and that relationships between children and their parents can be affected by atopic eczema. Children with atopic eczema are often more irritable and uncomfortable than unaffected children because of their skin condition and this can directly affect their behaviour. Sleep disturbance is very common among young children with eczema and many parents find it very difficult to cope with repeated nights of broken sleep. In addition, many parents find it difficult to manage scratching behaviour, which can lead to problems because the scratching can then become a way of controlling parental attention.[81] There is some evidence to suggest that mothers of children with atopic eczema feel less able to discipline their children than mothers of unaffected children.[83]

Seven studies described the measurement of psychological and psychosocial effects in children with atopic eczema and their families/carers (four case–control studies [EL = 2−] and two cohort studies and a case series [EL = 3]).[81,84-89] Severity of the atopic eczema varied in these studies. The studies either used assessment scales to measure the psychological effects of atopic eczema in children and their parents/carers or investigated attitudes and beliefs of children with atopic eczema and their parents/carers. The questionnaires were used once with no follow-up.

Personality Trait Inventory (PTI) and Childhood Psychopathology Measurement Schedule (CPMS)

The first case–control study compared the prevalence of psychological disorders in Indian children with atopic eczema with healthy controls. The study also considered whether mothers showed higher levels of emotional or mental distress.[84] [EL = 2−] The 22 children with atopic eczema diagnosed according to Rajka and Langeland's criteria were aged 3–9 years and attended an Indian paediatric dermatology clinic. Mild cases were excluded by including only children in whom the atopic eczema warranted outpatient hospital attendance every 3 months.

The tool used to assess psychological effects in the mothers was the Hindi adaptation of the Personality Trait Inventory (PTI). The mothers were asked to complete the proxy measure of the Childhood Psychopathology Measurement Schedule (CPMS) regarding their children. The study suggested that psychological disorders were more prevalent in Indian children with atopic eczema than controls and that mothers of children with atopic eczema were more submissive than mothers of children in the control group.[84] As this study used a Hindi adaptation of the PTI, it is not clear how these findings would relate to other populations.

Rutter A2 scale and General Health Questionnaire (GHQ)

The second case–control study evaluated the degree of psychological difficulties experienced by children with atopic eczema, 'mental distress' of the mothers, and family social support factors.[81] [EL = 2−] Thirty school-aged children (mean age 8.7 years, range 5.3–13.7 years) with any degree of atopic eczema, including very mild cases, and a control group of age–matched children with mild skin conditions (for example, warts) were recruited from hospital dermatology outpatient departments in the UK.

The children were assessed for psychological difficulties using the Rutter A2 scale. The mothers were assessed for mental distress using the General Health Questionnaire (GHQ). The study reported twice the rate of psychological disturbance in the children with atopic eczema compared with controls. This effect was statistically significant in children with moderate and severe atopic eczema, but not in those with mild atopic eczema ($P = 0.018$). Sleep disturbance was a problem in 67% of children with atopic eczema compared with 13% of controls ($P = 0.001$). Levels of mental distress were high in the mothers from both the atopic eczema and control groups, but the difference between the two groups was not significant ($P = 0.58$).

Children's Illness Perception Questionnaire (CIPQ) and Piers–Harris Children's Self-Concept Scale

The third case–control study investigated illness beliefs and psychosocial morbidity in children aged 7–12 years with atopic eczema ($n = 85$), asthma ($n = 45$) and no health problems ($n = 36$).[85] [EL = 2−] Children were recruited from paediatric hospital departments. No details of the severity of atopic eczema were reported. The Children's Illness Perception Questionnaire (CIPQ) and the Piers–Harris Children's Self-Concept Scale were used. Children completed the questionnaires without their parents' help in a room set aside within the hospital.

Children with atopic eczema felt greater consequences of their condition than those with asthma. Children's understanding of the disease was more strongly associated with psychosocial morbidity than the visibility of the condition.

Psychopathological diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association

The fourth study considered the psychiatric diagnosis in 490 children and young people with a variety of skin diseases, including 88 children with atopic eczema (mean age 9.1 years).[86] [EL = 3] The cohort consisted of children who had been hospitalised in an Italian paediatric dermatology department between 1997 and 2000. In some of these children, the clinical treatment of the skin disease warranted a psychological consultation and in others it was requested by a dermatologist (the study is therefore biased towards cases with psychological impairment). Diagnosis of psychopathology was based on criteria from the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association version 4 (DSM/IV) 1994. Atopic

eczema was associated with attention deficit/hyperactivity disorder (10%) and mental retardation (4%) in children aged 1–9 years; both of these disorders were reported only in males. Atopic eczema was associated with generalised anxiety disorder (13%) and dysthymic disorder (6%) in older children (aged 10–17 years); both of these disorders are found predominantly in young women. This study is problematic because of the lack of a control group and because of the highly unusual cohort of children with very-difficult-to-control atopic eczema. It is not possible, therefore, to generalise from this study to other groups of children with atopic eczema.

Hospital Anxiety and Depression Scale (HADS)

A further study investigated the effect of childhood atopic eczema and asthma on parental sleep and wellbeing.[87] [EL = 3] Ninety-two parents of 55 children with moderate to severe atopic eczema (n = 26) or asthma were asked to participate at atopic eczema and asthma outpatient clinics in the UK. The main outcome measures were sleep disturbance and the Hospital Anxiety and Depression Scale (HADS). Mothers caring for children with atopic eczema lost a median of 39 minutes of sleep per night and fathers lost a median of 45 minutes per night, whereas parents of children with asthma lost a median of 0 minutes sleep per night ($P < 0.001$). This finding was independent of age and whether the child had a one- or two-parent family. The depression score among mothers of children with atopic eczema was twice that among mothers of children with asthma (odds ratio (OR) 2.0, 95% CI 1.1 to 3.6, $P = 0.02$); multivariate analysis showed that this was due to lack of sleep rather that the child's atopic eczema *per se* (OR 1.1, 95% CI 0.5 to 2.4, $P = 0.8$).

Symptom Questionnaire (SQ)

One study used the Symptom Questionnaire (SQ) to investigate an educational and medical programme for children with atopic eczema and their parents.[88] [EL = 3] Seventeen families of children with atopic eczema aged 5–48 months were enrolled for six 2 hour sessions of an educational and medical programme. The SQ score decreased during the study (that is, the parents' levels of distress reduced during the intervention), but remained above those of parents of unaffected children. Educational interventions are discussed further in Section 8.1.

Child Behaviour Checklist (CBCL)

In one study, the parents of 74 children (mean age 7.1 ± 1.9 years), with mild, moderate and severe atopic eczema in equal numbers, were asked to fill in the Child Behaviour Checklist (CBCL), GHQ version 28, DFI and the Family Environment Scale (FES) by postal survey.[89] [EL = 3] CBCL data showed that 27% of the children were reported to have internalising behaviour problems and 10% were reported to have externalising behaviour problems compared with 18% and 17%, respectively, in the general population. Severity of atopic eczema (as determined by a dermatology consultant) was not significantly related to the children's internalising and externalising scores or parental psychological adjustment ($P > 0.05$). However, family adjustment (measured by DFI) was significantly related to the severity of atopic eczema ($P < 0.01$). Internalising behaviour scores and parental psychological wellbeing were positively associated with family impact ($P = 0.02$ for both); internalising behaviour scores and externalising behaviour scores were negatively associated with a supportive family environment ($P < 0.01$ and $P = 0.01$, respectively).

Studies evaluating the effectiveness of behavioural therapy for children with atopic eczema are considered in Section 7.10.

4.3 Assessment of quality of life

The impact of atopic eczema on quality of life in children and family members has been documented in several studies. Although atopic eczema is often not thought of as a serious medical condition it can have a significant negative impact on quality of life. A study looking at quality of life in children with chronic diseases showed that among chronic skin disorders atopic eczema and psoriasis had the greatest impact on quality of life, and only cerebral palsy scored higher than atopic eczema.[90]

Having a child with atopic eczema can affect many aspects of family life and the role of parenting.[83] A qualitative account of the experiences of mothers caring for children with severe atopic eczema showed that the extra work involved in caring for such children was not generated solely by treatment regimens, but rather by the overall burden of caring for the child and the extra housework generated by the disease.[91] An Australian study showed that caring for children with moderate to severe atopic eczema was more stressful for parents and families than caring for children with type 1 diabetes, citing direct financial costs, sleep deprivation, time missed from work, lost wages and potential parent 'unemployability' as factors.[7] Another study found 11 domains of life among parents to be affected, with the practical difficulties of caring for children with atopic eczema being the most problematic (74%) and the second most important aspect after the children's ability to cope with atopic eczema. Exhaustion, anxiety and guilt were reported in 71% of parents.[92]

Several surveys have highlighted the impact of atopic eczema on loss and/or quality of sleep.[93-95] A survey of sleep difficulties in preschool children with atopic eczema reported problems in 85% of 39 parents of children experiencing atopic eczema flares, with an average of 2.7 wakings per night and total sleep loss of 2.6 hours per night.[93] [EL = 3] A survey conducted in the UK by the National Eczema Society showed that 60% (n = 1176) of children questioned (83% younger than 11 years and 55% of school age) reported their sleep patterns to be affected by their atopic eczema.[94] [EL = 3] A study of 429 US children (15 years or younger) reported that 80% rated their disruption of sleep as 'somewhat' or 'a lot'. Thirty percent used medication to aid sleep.[95] [EL = 3]

The 2004 International Study of Life with Atopic Eczema (ISOLATE) surveyed the effects of atopic eczema on the lives of patients and society (n = 2002, of which 40% were carers of children aged 2–13 years).[96] [EL = 3] For children under 13 years, atopic eczema affected sleep for an average of five nights during a flare; the average number of wakings per night was 1.8. Thirty-nine percent of respondents reported that atopic eczema affected other household members. Analysis based on the Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD; see below for further details) confirmed the negative effect of atopic eczema on patients and caregivers. Seventy-five percent of caregivers felt that being able to effectively control atopic eczema would be the single most important improvement to their own quality of life or that of their children.[96]

Further research has described other factors that have contributed to the stress of caring for children with atopic eczema, reporting that mothers were less likely to be in employment outside the home and had less support in their social life, with friends being unwilling to offer to look after their children. Families were often restricted socially in their choice of restaurants and holidays.[97]

Studies considered in this section

No studies were found that addressed the utility of quality of life scales in routine clinical practice. Studies describing the validation of five dermatology-specific scales or indexes for measuring quality of life in children with atopic eczema and/or their families/carers were identified (Table 4.3). Of the five, two measured quality of life only in children (Infants' Dermatitis Quality of Life (IDQoL) index, a proxy measure completed by parents, and CDLQI), two measured quality of life only in parents and other family members (DFI and PIQoL-AD), and one measured quality of life in children and their parents/families (Childhood Atopic Dermatitis Impact Scale (CADIS)). All except the CDLQI were specific to atopic eczema. Studies designed to validate the five quality of life tools (by examining validity, reliability, responsiveness and acceptability) are described in this section. The questionnaires for IDQoL, CDLQI and DFI are available at www.dermatology.org.uk. Although some English language publications describing studies using the German scale *Fragebogen zur Lebensqualität von Eltern neurodermitiskranker Kinder* (FEN; a measure of quality of life in parents of children with atopic eczema) were identified,[98-101] no English language publications describing the development or validation of FEN were identified and so this scale is not considered further.

Further studies that used IDQoL, CDLQI or DFI to evaluate interventions for atopic eczema are described in Chapter 7. It is recognised that such studies also provide some validation of the tools, although the studies were not designed for this purpose.

Table 4.3 Summary of dermatology-specific quality of life scales that have been evaluated for use in children and/or their parents or caregivers

Scale	Description
Infants' Dermatitis Quality of Life (IDQoL) index	A condition-specific proxy measure of the quality of life impact of atopic eczema in infants and children aged 0–4 years. It comprises a one-page questionnaire with ten questions pertaining to the previous week, derived from parental information about the impact of atopic eczema plus an additional question on parent's perception of global severity. It is similar in format and scoring to the CDLQI. The maximum score is 30, and the greater the score the greater the impact on quality of life. It is available in 15 languages.
Children's Dermatology Life Quality Index (CDLQI)	A dermatology-specific measure of the quality of life impact of any skin disease on children aged 4–16 years. It comprises a ten-question scale in written or cartoon form which assesses the domains of physical, social and psychological impact (symptoms and emotions, social relationships, schooling, recreation, sleep and treatment difficulties) of atopic eczema over the previous week. Each question has four answers: not at all = 0, a little = 1, a lot = 2, very much = 3. Thus 0 is the best score and 3 the worst score. The maximum score is 30. It is available in over 20 languages.
Dermatitis Family Impact (DFI) scale	A condition-specific scale that measures the impact of childhood atopic eczema on family life over the previous week and is based on ten items: housework, food preparation, sleep of other family members, leisure activities such as swimming, time spent on shopping, costs related to treatment or clothes, tiredness or exhaustion, emotional distress, relationships in the family, and the impact of helping with treatment on the life of the main carer. It is a one-page questionnaire. Scoring is similar to that of the CDLQI.
Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD)	A dermatology-specific scale to assess the quality of life of parents of children with atopic eczema. It adopted the needs-based model of quality of life which postulates that life gains its quality from the ability and capacity of individuals to fulfil their needs. According to this model, functions such as physical activities, hobbies and socialising are important only insofar as they provide the means by which needs are fulfilled. It consists of 28 items with a dichotomous response format (i.e. score 0–28).
Childhood Atopic Dermatitis Impact Scale (CADIS)	A hypothesis-based quality of life survey to measure the impact of atopic eczema on children aged up to 8 years and their families. It covers four domains (physical health, emotional health, physical functioning, and social functioning). It is a 45-item scale using a five-category choice method (score 0–180).

Infants' Dermatitis Quality of Life (IDQoL) index

The IDQoL index was constructed by an initial pilot study using data obtained from over 70 parents and tested in the community, although the data were published only in the form of an abstract. Minor changes were made for clarity and then a validation study was undertaken in which parents of 102 children with atopic eczema under the age of 4 years were recruited by post (n = 34) or via an outpatient department (n = 68).[102] [EL = 3] The outcome measures in this study were IDQoL, the DFI and the Infants' Behavioural Check List (BCL). One of the main aims of the study was to revalidate the DFI. Parents were asked to complete the questionnaires at two different times, either in the clinic and then at home within 8–24 hours or both copies at home with an 8–24 hour break in-between. The mean score was 7.89 (standard deviation (SD) 5.74) for the IDQoL and 8.87 (SD 7.06) for the DFI. The highest scoring questions for the DFI were parental sleep disturbance (1.22, SD 1.01), tiredness and exhaustion (1.22, SD 1.02) and emotional distress (1.11, SD 0.98). The highest scoring questions for the IDQoL referred to itching and scratching (1.62, SD 0.82), mood change (1.10, SD 0.99) and sleep disturbance (0.91, SD 0.98). Post-treatment questionnaires from 25 patients indicated sensitivity to clinical change with both IDQoL and DFI. Correlation between the IDQoL and DFI was high (r = 0.87). (Correlation between the DFI and clinical severity was lower; r_s = 0.5. Good test–retest reliability of the DFI was also shown through correlation of first and second assessments of the DFI; r = 0.95, n = 72).

A further validation of the IDQoL and the DFI was carried out via an audit of the impact of a paediatric dermatology consultation for a group of 203 infants with atopic eczema.[103] [EL = 3]

The mean score was 8.47 for both IDQoL and DFI (SD 5.8 and 6.5, respectively). These scores showed good correlation with each other (r_s = 0.79, 95% CI 0.73 to 0.84). The highest scoring IDQoL items were itching and scratching, problems at bath time and time to fall asleep. The highest scoring DFI items were tiredness and exhaustion, sleep loss and emotional distress. These items also correlated most strongly with eczema severity for both IDQoL and DFI. Fifty parents in this study completed questionnaires at their first and second visits: median IDQoL scores fell from 8 to 5, median DFI scores fell from 9 to 3, and median eczema severity scores fell from 2 to 1). The IDQoL items that showed greatest improvement were time taken to get to sleep and difficulties at mealtimes; the DFI items that showed greatest improvement were tiredness, exhaustion and emotional distress in parents.

Children's Dermatology Life Quality Index (CDLQI)

Five studies described the development and validation of the CDLQI in its written form.[75,82,90,104,105] A further study validated a cartoon version of the CDLQI.[106]

The initial development and validation of the CDLQI involved 169 children aged 3–16 years who attended a paediatric dermatology clinic. They were asked to write down, with their parents' help, the ways in which their skin disease affected their lives.[82] [EL = 3] One hundred and eleven different aspects were identified. Ten questions were then composed to cover these aspects, using a structure similar to the adult Dermatology Life Quality Index. The draft questionnaire was piloted with 40 children and then minor alterations were made to improve clarity. The CDLQI questionnaire was then given to a further 233 dermatology paediatric outpatients (mean CDLQI score 5.1, SD 4.9), and to 102 controls (47 siblings attending the clinic and 55 children attending a general paediatric clinic; mean CDLQI scores 0.4, SD 0.7 and 0.7, SD 2.5, respectively). The CDLQI scores for atopic eczema (mean 7.7, SD 5.6, n = 47), psoriasis (mean 5.4, SD 5.0, n = 25) and acne (mean 5.7, SD 4.4, n = 40), were all significantly greater than for moles and naevi (mean 2.3, SD 2.9, n = 29). The highest scoring questions related to symptoms (mean score 1.05, n = 233), feelings (mean score 0.9), swimming and sports (mean score 0.51), sleep (mean score 0.49) and treatment effects (mean score 0.47), with the question on effects on friendships (mean score 0.18) scoring least. The test–retest reliability of the questionnaire was checked by asking 46 patients to complete the CDLQI on two occasions; the test–retest mean difference was 0.28. The questionnaire is designed to be completed by the child.

The CDLQI has also been used in a study determining a relationship between the quality of life of children with atopic eczema and disease severity.[75] [EL = 3] Seventy-eight children (mean age 8.6 years) attending their first assessment were asked to complete the CDLQI. Eczema severity was assessed using the SCORAD index. Ninety-one percent (71) of the children attended a second visit and were included in the analysis. The CDLQI was significantly correlated with SCORAD at the first and second visits (r = 0.52 and r = 0.59, respectively; P < 0.001 for both). Each unit change in SCORAD was associated with a 0.12 unit change in the children's quality of life (95% CI 0.04 to 0.19, P = 0.004). Itching had the highest impact on the children's quality of life (mean score 1.17 at the first visit and 0.82 at the second visit, P = 0.008). Concerns about sleep had the second highest mean score (0.43 at the first visit and 0.38 at the second visit, P = 0.8).

In a cross-sectional study involving 80 children with atopic eczema (mean age 11.7 ± 3.7 years), CDLQI scores were compared with SCORAD and NESS scores for the severity of the atopic eczema.[105] [EL = 2–] CDLQI scores had a low correlation with SCORAD and NESS scores (Spearman's coefficient ρ = 0.23 and 0.29, respectively, P < 0.05). There was no correlation between CDLQI and the objective SCORAD score (Spearman's coefficient ρ = 0.17, p>0.05). The authors concluded that quality of life and severity scores for atopic eczema should be considered separately in the assessment of atopic eczema in children.

Further validation of the CDLQI was conducted in a study where the generic, proxy measure CLQI was used in children with a variety of skin diseases.[90] [EL = 3] The CDLQI was completed by 379 children aged 5–16 years with skin disease of more than 6 months' duration. The children's parents (n = 379) and parents of 160 children aged 5–16 years with other chronic diseases were asked to complete the CLQI. In the children's opinion, atopic eczema and psoriasis caused the greatest impairment of all common skin conditions (CDLQI scores representing 30.5% and

30.6%, respectively, of the total possible score). Using the CLQI, the highest score was atopic eczema (33%). The CDLQI and the CLQI showed a strong linear association (r_s = 0.72, P < 0.001) and reasonably good agreement (expressing scores out of 100, the 95% limits of agreement ranged from −25.5% to 26.7%).

A cartoon version of the CDLQI was validated against the written version in a further study comprising three parts.[106] [EL = 3] In the first part, 101 children (median age 11 years) with a variety of dermatological conditions (atopic eczema 17%) completed both versions of the CDLQI in random order in an outpatient setting; a further 66 children completed the cartoon version in the outpatient setting and at home on the same day, returning the questionnaire completed at home by post. In the second part, under more controlled conditions, both versions of the CDLQI were administered in random order to 107 children (median age 11 years, atopic eczema 20%). The time to complete each questionnaire and children's and parents' preferences were recorded. The third part assessed adherence by asking 546 children (median age 12 years) whose atopic eczema had been reviewed recently in dermatology clinics to complete and return a single postal CDLQI (either the cartoon or written version). There was no significant difference in scores between the versions in parts 1 and 2, but the cartoon version was completed faster than the written version (90 seconds versus 120 seconds, P < 0.0001). Children and parents preferred the cartoon version and found it easier to use. Forty-six per cent of postal questionnaires were returned with approximately equal numbers of cartoon and written versions.

A further study assessed the impact of atopic eczema on family quality of life using a Malay version of the CDLQI, the DFI and the SCORAD index.[104] [EL = 3] Parents of 70 children (mean age 74 months) completed the study. Assessments were made at two visits conducted 2 weeks apart. The mean SCORAD index was 38.9 (SD 15.5) at the first visit and 34.6 (SD 16.4) at the second visit (P = 0.003). Thirty-three patients aged 7 years or over completed the CDLQI questionnaire. The mean CDLQI score was 10.0 (SD 6.6) at the first visit and 7.6 (SD 6.2) at the second visit. Children with mild atopic eczema scored 6.5 (SD 7.8, n = 2), those with moderate eczema scored 8.8 (SD 5.9, n = 21), and those with severe eczema scored 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). Seventy parents completed the DFI questionnaire. The mean DFI score was 9.4 (SD 5.3) at the first visit and 7.8 (SD 4.8) at the second visit. The DFI scores for families of children with moderate atopic eczema were significantly lower than those for families of children with severe atopic eczema (moderate 8.5 (SD 5.1, n = 38) versus severe 11.5 (SD 5.2, n = 27), P = 0.02). The highest scoring items for the DFI differed from those for the CDLQI; they were sleep loss (1.23, SD 0.9), parents' emotional disturbance (1.1, SD 0.9), exhaustion (1.1, SD 0.9) and questions regarding diet and treatment (1.0, SD 0.8).[104]

Dermatitis Family Impact (DFI) scale

Three studies have outlined the development and validation of the DFI scale[92,102,103] and two further studies have related the DFI to the severity of atopic eczema in children.[74,104]

The initial development and validation of the DFI scale involved ethnographic interviews of 34 families, which led to the identification of 11 basic problem areas from which a detailed 102-item questionnaire was constructed. The questionnaire was then trialled on 52 families of children with atopic eczema, either in clinic or by post, and a shorter (one-page) ten-question DFI questionnaire was designed (maximum score = 30).[92] [EL = 2−] From the utility questions the three factors rated by parents as being most important were (in decreasing order of importance) the child's ability to cope with the disease, practical care issues, and satisfactory family relationships. Sixty-eight percent of families had experienced sleep disturbance in the previous week. Financial aspects were generally rated low, but 11% of parents felt their lifestyle had been changed because of the financial burden of the atopic eczema. Finally, the ten-item questionnaire was posted to 50 families of children with atopic eczema and 50 families of children under 12 years who had no history of atopic disease. The mean DFI score in the atopic eczema group was significantly greater than that in the families with unaffected children (mean scores 9.6 ± 7.0 (range 0–27, n = 56) versus 0.4 ± 0.9 (range 0–3, n = 26), P < 0.0001). The highest scoring questions were treatment, tiredness and distress.

The second and third studies that evaluated the development and validation of the DFI were described in the section on IDQoL.[102,103]

The first study that related the DFI to the severity of atopic eczema in children was described in the section on CDLQI.[104] The second such study used the modified SCORAD index (SCORAD-D) to measure severity.[74] [EL = 3] In this study, 106 children with atopic eczema (age range 5–10 years) were assessed during two dermatology visits conducted 6 months apart. At the first visit, 80% of the children were diagnosed as having mild atopic eczema and the family quality of life was affected in 45% of cases. The mean DFI score was 2.4 (SD 4.4) and the mean SCORAD-D score was 8.2 (SD 10.2). In 24 (23%) of the children the atopic eczema had affected sleep in other family members. At the second visit, family quality of life was affected in 36% of cases, the mean DFI score was 1.9 (SD 4.2) and the mean SCORAD-D score was 7.7 (SD 8.7). Changes in the DFI score were positively associated with changes in the SCORAD-D score (regression coefficient 0.17, 95% CI 0.06 to 0.29, $P = 0.002$).

Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD)

One publication described the international development of the PIQoL-AD.[107] The clinical significance of the PIQoL-AD was discussed in a further publication that described four randomised controlled trials (RCTs) involving pimecrolimus (a topical calcineurin inhibitor).[108] Both studies are described below. Further studies have used PIQoL-AD as an outcome measure but did not evaluate the measure itself.[96,109,110]

The first publication described how the content of the PIQoL-AD instrument was derived from 65 qualitative interviews with parents in the UK, the Netherlands and Italy.[107] [EL = 3] The measure was then produced for seven European countries and field-testing interviews were used to assess face validity and content validity. Insufficient data from one country meant that the PIQoL-AD was only assessed further in the six remaining countries. Surveys were conducted at two time points in each of the six countries to finalise the instrument, with between 45 and 328 children and their parents taking part in each country. This study resulted in a final 28-item PIQoL-AD questionnaire which showed good item fit, test–retest reliability (≥ 0.85) and internal consistency (Cronbach's coefficients 0.88–0.93 in both surveys).

PIQoL-AD scores from four RCTs evaluating the effectiveness of pimecrolimus 1% cream (total $n = 621$ children with atopic eczema and their parents) were interpreted in one publication.[108] [EL = 1+] Anchor- and distribution-based statistical methods were used to interpret the clinical significance of the PIQoL-AD measurements. Anchor-based methods examine the relationships between scores on a test instrument (that is, the PIQoL-AD) and an independent anchor (usually a clinical measure of disease severity). PIQoL-AD data were combined for all time points from the four RCTs using anchor-based analysis to give combined means, medians, SDs and 95% CIs for each disease severity categories in the following instruments: EASI, IGA, pruritus severity and Subject's Assessment (SA). A significant progression in mean PIQoL-AD scores with increasing severity of disease was shown ($P < 0.01$ for all), although correlation was weak.

Distribution-based methods determine clinical significance based on statistical distributions of the instrument scores used in a given study. The distribution-based method used to evaluate change in the PIQoL-AD scores was the effect size (measure of change over time), which was similar over all four RCTs. A change in PIQoL-AD scores of 2–3 points over time would be considered to be clinically significant and thus to be of use for clinical practice. This scale is, however, not available for general use in the UK.

Childhood Atopic Dermatitis Impact Scale (CADIS)

Two studies have described the development and validation of the CADIS.[111,112] [EL = 3]

The first study described how the effects of atopic eczema on young US children and their families were documented to devise a conceptual framework from which quality of life instruments could be developed.[111] [EL = 3] Directed focus sessions were performed with parents of 26 young children with atopic eczema (mean age 23 months, range 3–69 months) and six experts. Parents and experts mentioned a total of 181 specific quality of life effects from which a conceptual framework comprising domains related to physical health, emotional health, physical functioning and

social functioning was devised. Each domain included effects on the children and their parents. Of particular note were the sleep problems described by 22 of the 23 families interviewed.

The second study, which was based on the conceptual framework from the above study and involved 270 children with atopic eczema (mean age 16 months) and their parents, tested and validated the CADIS.[112] [EL = 3] Exploratory factor analysis eliminated nine items, Rasch analysis eliminated a further three items and parental responses to the questionnaire eliminated five further items, which resulted in a five-scale framework. The three most common problems for both children and parents were itching/scratching (85%), pain/discomfort (12%) and sleep issues (10%). Internal consistency was acceptable for all five scales (Cronbach's α = 0.91 for family and social function, α = 0.92 for emotion; α = 0.76 for sleep, α = 0.93 for symptoms, and α = 0.84 for activity and behaviour).

Evidence statement for assessment of severity, psychological and psychosocial wellbeing and quality of life

Severity

A number of different measurement instruments have been described for assessing disease severity in children with atopic eczema. The majority of named measurement instruments are based on visual assessments of clinical signs and disease extent, although some involve the assessment of patient symptoms. The SCORAD and EASI instruments are the tools that have been validated most extensively in the research setting, although significant inter-observer variability has been observed with both instruments. [EL = 3]

No studies have considered the clinical utility of different instruments for measuring the severity of atopic eczema in routine clinical practice (that is, the usefulness of individual instruments or whether basing treatment decisions on measurements obtained with any instrument improves clinical outcomes for people with atopic eczema and their parents/families).

Psychological and psychosocial wellbeing and quality of life

Limited data from questionnaire studies show that children with atopic eczema are at increased risk of developing psychological problems compared with children who do not have the condition. There is some evidence that the psychological impact is greater in those with moderate to severe disease compared with mild disease. [EL = 3]

Validated quality of life scales have been used to assess the quality of life of children with atopic eczema and of their parents. The children's quality of life scales rate symptoms and signs (itching and scratching), feelings (mood change), involvement in sport, sleep and treatment effects as the most important factors of living with atopic eczema. The parents'/families'/caregivers' quality of life scales suggest that the psychological burden of care is related to the children's atopic eczema directly and indirectly (e.g. through sleep disturbance). [EL = 3]

There was no evidence examining the usefulness of quality of life measures in guiding treatment decisions and clinical practice.

In studies in which both severity and quality of life have been measured, a significant correlation has been shown between severity of atopic eczema and impact on quality of life. It has also been shown that atopic eczema has a greater impact on quality of life than many other chronic conditions, including asthma and type 1 diabetes. [EL = 3]

Cost-effectiveness

No published evidence relating to the cost-effectiveness of assessing severity, psychological health or quality of life was identified.

None of the clinical studies described above addressed the usefulness of measuring severity of atopic eczema in routine clinical practice. While the purpose of assessing severity is to inform clinical management, there is no evidence of how this assessment improves the management of atopic eczema or leads to better health outcomes for the children. Without this information, it is not possible to assess whether the time taken to complete a severity questionnaire (which could take up a considerable part of a consultation) is a good use

of a healthcare professional's time, or whether this time would be more usefully spent on other tasks to improve patients' health. Evaluative studies that can follow through assessment of severity with changes in clinical management and health outcome are required in order to assess the cost-effectiveness of this type of assessment in routine clinical practice.

One study of quality of life was undertaken for use in cost-effectiveness research of children with atopic eczema and to calculate the quality-adjusted life years (QALYs) associated with the disease in children.[113] QALYs value health states from 0 (states as bad as death) to 1 (perfect health). The worst health state for atopic eczema was valued at 0.36 of a QALY (SD 0.36), and the best heath state at 0.84 (SD 0.19), which can be interpreted as a 16% loss in quality of life.

From evidence to recommendations

The GDG believes that assessing the severity of atopic eczema and the quality of life of children and their families/carers allows more effective treatment decisions to be made. It is the view of the GDG that the child's and/or parent's/carer's perception of the severity of their condition can be obtained by asking questions about the skin and quality of life, including psychosocial wellbeing. Structured, validated tools can provide additional useful information in certain circumstances, for example in prompting children or their families/carers for information regarding their condition, thereby improving communication and, ultimately, treatment decisions.

The treatment of atopic eczema revolves around alleviating symptoms. It is the GDG's view that children and their parents/carers should also be asked specifically about itch and sleep because they appear to be the most important parameters to be considered when measuring disease severity.

In the absence of standardised definitions of clear, mild, moderate and severe atopic eczema, definitions of these terms were agreed by GDG consensus. Active atopic eczema is taken to mean evidence of the signs and symptoms associated with mild, moderate and/or severe atopic eczema. The GDG also proposed categories for the impact that atopic eczema has on quality of life and psychosocial wellbeing. The GDG believes that it is possible for a child's skin to be classified as mild atopic eczema yet have a severe impact on quality of life, and vice versa. The consensus view of the GDG is that it is helpful for children with atopic eczema and their parents or carers to know the overall severity of the disease and so this information should be communicated to them.

The GDG considered availability, ease of use and validity of the available tools to determine which to recommend for use in clinical practice. The following severity tools were ruled out because they were too complicated, required special equipment or training or did not have enough validation data to support their use: ADAM, BCSS, Costa's SSS, EASI, OSAAD, SASSAD, SCORAD, the Skin Detectives Questionnaire and TIS. NESS was considered easy to use but not relevant to everyday clinical practice. IGA was found to be useful, but the GDG considered POEM to be the best tool as it was short, easy for parents or caregivers to complete and easily accessible via the internet. The quality of life tools CADIS and PIQoL-AD were ruled out because they were too lengthy and too complicated to use in routine clinical practice. The GDG considers IDQoL, CDLQI and DFI to be viable options for the assessment of quality of life in infants, older children and families, respectively, because they are all easy to complete and are easily accessible via the Internet.

Recommendations for assessment of severity, psychological and psychosocial wellbeing and quality of life

Healthcare professionals should adopt a holistic approach when assessing a child's atopic eczema at each consultation, taking into account the severity of the atopic eczema and the child's quality of life, including everyday activities and sleep, and psychosocial wellbeing (see Table 4.4). There is not necessarily a direct relationship between the severity of the atopic eczema and the impact of the atopic eczema on quality of life.

Table 4.4 Holistic assessment

Skin/physical severity		Impact on quality of life and psychosocial wellbeing	
Clear	Normal skin, no evidence of active atopic eczema	None	No impact on quality of life
Mild	Areas of dry skin, infrequent itching (with or without small areas of redness)	Mild	Little impact on everyday activities, sleep and psychosocial wellbeing
Moderate	Areas of dry skin, frequent itching, redness (with or without excoriation and localised skin thickening)	Moderate	Moderate impact on everyday activities and psychosocial wellbeing, frequently disturbed sleep
Severe	Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation)	Severe	Severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep

Healthcare professionals should explain the overall physical severity of a child's atopic eczema to the child and their parents or carers.

Healthcare professionals should be aware that areas of atopic eczema of differing severity can coexist in the same child. If this is the case, each area should be treated independently.

During an assessment of psychological and psychosocial wellbeing and quality of life, healthcare professionals should take into account the impact of atopic eczema on parents or carers as well as the child and provide appropriate advice and support.

Healthcare professionals should be aware that all categories of severity of atopic eczema, even mild, can have a negative impact on psychological and psychosocial wellbeing and quality of life. This should be taken into account when deciding on treatment strategies.

Healthcare professionals should consider using the following additional tools to provide objective measures of the severity of atopic eczema, quality of life and response to treatment:

- visual analogue scales (0–10) capturing the child's and/or parents' or carers' assessment of severity, itch and sleep loss over the previous 3 days and nights
- validated tools:
  - Patient-Oriented Eczema Measure (POEM) for severity
  - Children's Dermatology Life Quality Index (CDLQI), Infants' Dermatitis Quality of Life index (IDQoL) or Dermatitis Family Impact questionnaire (DFI) for quality of life.

Research recommendations for assessment of severity, psychological and psychosocial wellbeing and quality of life

Does the use of severity tools in the assessment of atopic eczema in children in routine practice improve clinical management and outcome (aiding decisions on treatment strategies, increasing clinical response) and is this a cost-effective use of clinical time?

Why this is important
Assessing the severity of eczema is very difficult to do but is essential in guiding management of the disease. Easy-to-use validated methods are required in order to aid clinical management in a cost-effective way.

What is the optimal method (in terms of ease of use, accuracy and sensitivity) of measuring the severity of atopic eczema in children in routine clinical practice?

Why this is important
The majority of instruments for measuring the severity of atopic eczema in children have been developed and validated for clinical research rather than for routine clinical practice. There is

a need for studies comparing the available measurement instruments in routine clinical practice where the spectrum of disease severity and time available for measurements may differ significantly from the research setting.

Which psychological and quality of life scales are the most appropriate for use in clinical practice in children with atopic eczema in terms of guiding management or for outcomes of treatment and is their use effective and cost-effective?

Why this is important
Eczema can have a detrimental psychological effect on children and also impair their quality of life. Measurement tools can ascertain the level of effect and whether or not treatment improves it but many are too cumbersome and time-consuming to use in a clinical setting. Research is required to ascertain the usefulness and cost-effectiveness (clinical time) of using such validated tool in a clinical setting and which are quick and simple to use, giving reproducible results.

5 Epidemiology

Studies considered in this chapter

Studies focusing on the epidemiology of atopic eczema in children (prevalence, age of onset and resolution, frequency, location and extent of flares, associations with asthma, hay fever and food allergies, and variations in different ethnic groups) as their prime objective were considered for this section. Preference was given to reviews of observational studies and to data from the UK. Where data from the UK were not available, studies conducted in other countries were included. It is recognised that some epidemiological data may be reported in other publications which are not considered here because their primary objectives did not include investigation of the epidemiology of atopic eczema in children.

Overview of available evidence

Two reviews that were published as chapters in textbooks were identified. Literature searches for both reviews were undertaken systematically, but the eligibility criteria were not stated and therefore the reviews have been given a low evidence level.[114,115] [EL = 3]

Point prevalence

Several studies have considered the epidemiology of atopic eczema in children. However, differences in study populations evaluated, in the definition of atopic eczema and in survey methods result in a wide range of prevalence estimates.

A review (end search date year 2000) found 30 studies that measured the prevalence of atopic eczema in the 1990s, 26 of which included children aged up to 12 years (solely or predominantly).[114] In the five studies conducted in the UK (1992 to 1996), point prevalence rates ranged from 5.9% (using the UK Working Party Diagnostic Criteria in 3- to 11-year-olds, *n* = 1523) to 14.2% (dermatologist's examination in 4-year-olds, *n* = 260). [EL = 3]

Two studies provided some data for trends in point prevalence rates over time for the UK, one of which was recently updated.[116,117] One reported that in children aged 12 years in South Wales the prevalence of ever having had atopic eczema increased from 15.9% in 1988 to 23.1% in 2003 (*n* = 1148).[117] The second study, in children aged 8–13 years in Aberdeen, found that the point prevalence of eczema increased from 5.3% in 1964 to 12% in 1989 (*n* = 2510 and 3403, respectively).[116]

Studies in Scandinavia, Germany and Japan that considered point prevalence or cumulative incidence of atopic eczema in children of the same age (6, 7, or 7–13 years) born in different years showed that the prevalence increased from the 1980s to the 1990s. The increases were from 8.6% to 13% in 6-year-olds,[118] 18.9% to 19.6% in 7-year-olds,[119] 13.2% to 19.7% in 7- to 13-year-olds,[120] 15% to 22.9% in 7- to 12-year-olds,[121] 8.6% to 11.8% in 9-year-olds,[118] and 9.6% to 10.2% in 12-year-olds.[118] [EL = 3]

Period prevalence

Two studies reported period prevalence of atopic eczema in children in the UK. A 1 year period prevalence of 11.5% was reported for schoolchildren aged 3–11 years in Birmingham (*n* = 1077).[122] In a study in children aged 1–5 years, the 1 year period prevalence was 16.5% (*n* = 1523).[123] The International Study of Asthma and Allergies in Childhood (ISAAC) found that the 12 month period prevalence in 6- to 7-year-olds in the UK was 13% (*n* = 1864). The worldwide figures ranged from under 2% in Iran to over 16% in Japan and Sweden (*n* = 256 410 in 90 centres).[124,125]

In a cohort of children in the UK followed from birth to 10 years of age, the period prevalence of atopic eczema was 9.6% at age 1 year, increasing to 10.3% at 2 years, 11.9% at 4 years and 14.3% at 10 years. Lifetime prevalence of atopic eczema was 41% at 10 years of age. Of the 41% of children who had ever had atopic eczema, 56.3% still had the condition at age 10 years

(*n* = 1456).[126] Another UK cohort study found that lifetime prevalence was 25.3% at age 8 years, with annual point prevalence ranging from 8.3 to 10.6%.[127] [EL = 3]

Geographical variation in prevalence

Data from the 1958 British Birth Cohort study, showed regional differences in prevalence (*n* = 8278). The lifetime prevalence of parent-reported eczema (it was not stated whether the eczema was atopic) in 7-year-old children ranged from 5.3% in the North-West region of England to 10.8% in the Eastern region (prevalence rates in Scotland and Wales were within this range). The point prevalence of eczema examined by school medical officers was lower than for parent-reported eczema, ranging from 1.7% to 4.7%.[128] [EL = 3] It is not known whether these regional prevalence figures reflect current patterns. The ISAAC study did not report prevalence rates by region. Potential reasons for geographical differences in the prevalence of atopic eczema could include differences in social class, pollution and water hardness. Factors that might trigger exacerbations of established atopic eczema are considered in Section 6.1.

Prevalence in different ethnic groups

Two observational studies from the UK considered the epidemiology of eczema in different ethnic groups. The first reported the prevalence of atopic eczema in Asian and non-Asian children in Leicester (*n* = 413).[129] The study found no difference in the point prevalence or lifetime prevalence of atopic eczema in Asian and non-Asian children:

- point prevalence 9% versus 11%, 95% CI for the difference −3.8% to 8.9%
- lifetime prevalence 16% versus 15%, 95% CI for the difference −7% to 7%.

Similarly there was no significant difference in the severity of atopic eczema between Asian and non-Asian children (mean SASSAD score 6.3 (SD 3.7) versus 7.3 (SD 3.5)).[129] [EL = 3]

In schoolchildren aged 3–11 years in London, the point prevalence of atopic eczema diagnosed by a paediatric dermatologist was 11.7% (*n* = 693). The prevalence appeared to be higher in black Caribbean children than in white children, although the statistical significance of this was dependent on the criteria used to diagnose the eczema (statistically significant for the dermatologist's diagnosis, parental report and the criterion 'history of flexural itchy rash', but not statistically significant when the sign visible flexural dermatitis was considered).[130] [EL = 3]

Incidence and age of onset

A UK study considered the incidence of atopic eczema in children aged up to 2.5 years born in 1991 and 1992. The incidence was highest during the first 6 months of life (21%), falling to 11.2% by the age of 6–18 months, and to 3.8% by the age of 30 months (2.5 years). The corresponding period prevalence rates were highest at age 6–18 months (25.6%) compared with 21% at 0–6 months, 23.2% at 18–23 months, and 19.9% at 30–42 months (2.5–3.5 years; *n* = 8530).[131] [EL = 3]

The age of onset of atopic eczema was considered in one of the reviews,[115] which identified eight studies published between 1948 and 1989. The countries where the studies were conducted were not made clear. The data were derived from individuals who were hospitalised or attending specialist clinics. The age of onset of atopic eczema was less than 1 year in between 42% (*n* = 100) and 88% (*n* = 121) of individuals (the age at follow-up was up to 50 years).[115] [EL = 3] In a UK community cohort study (the 1958 British Birth Cohort study) which was included in the review, 66% of those with examined or reported atopic eczema at the age of 16 years had developed the condition by the age of 7 years (*n* = 1053).[115,132] [EL = 3]

A further five observational studies conducted in the UK were identified.[95,122,126,127,133] [EL = 3] Three of the studies considered the age at presentation with eczema and made the following observations:

- atopic eczema had presented during the first year of life in 68% of children aged 5–10 years with the condition (*n* = 137; recruited from general practice); children who developed atopic eczema during the first year of life were more likely to have severe eczema (adjusted OR 2.1, 95% CI 1.2 to 3.2)[133]
- 71.0% of children aged 10 years who had atopic eczema symptoms in the previous year had first developed atopic eczema before the age of 4 years (*n* = 1456)[126]
- the median age at onset was 6 months in children aged 3–11 years (*n* = 1077; 204 with eczema).[122] [EL = 3]

Two of the studies considered the age at which the diagnosis was made:

- in children with atopic eczema aged 15 years or under, 93% of diagnoses were made in the first 2 years of life (*n* = 429)[95]
- in a birth cohort, 56.7% of those aged 8 years who had ever been diagnosed with atopic eczema were diagnosed by the age of 2 years (*n* = 592).[127] [EL = 3]

Disease severity

Epidemiological data from studies involving several countries collated in one of the reviews[114] showed that 65–90% of community cases of atopic eczema were of mild severity, with only 1–2% classified as severe. It was noted that there was a lack of data relating severity of atopic eczema to age.[114] [EL = 3]

In children aged 1–5 years in the UK, 84% were considered to be mild, 14% moderate, and 2% severe (*n* = 1760, dermatologist's rating).[123] In older children in the UK (aged 5–10 years), similar figures were reported using the SCORAD instrument: atopic eczema was mild in 80% of children, moderate in 18% and severe in 2% (*n* = 137).[133] The ISAAC study reported that the 12 month period prevalence of severe eczema in the UK was 2.0%.[124]

Prognosis

One of the reviews[115] identified 25 studies that investigated the long-term prognosis of atopic eczema, 22 of which included children aged under 12 years at study inception (studies were reported between 1930 and 1997). Only data from studies that included children at inception were considered here. The countries in which the studies were conducted were not made 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 and losses to follow-up were common, ranging from about 3% to 73% (median 31%). The studies identified atopic eczema as a chronic condition with a 10 year clearance rate of 50–70%, although a wide range of clearance rates over varying follow-up periods were 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.[115] [EL = 3] The general findings of this review should be treated with caution because studies with prognostic data from decades ago may not be directly transferable to the present day owing to changes in factors affecting the condition. [EL = 4]

The British Birth Cohort study reported that, of the children with atopic eczema at age 7 years, 65% were clear of reported or examined eczema at the aged of 11 years, and 74% at the age of 16 years. However, these apparent clearance rates fell to 53% and 65%, respectively, when adjusting for subsequent recurrences in teenage years or adulthood (*n* = 571).[132]

One further study considered prognosis. In children in Germany who developed atopic eczema before the age of 2 years, 43.2% were in 'complete remission' by the age of 3 years, 38.3% had an intermittent pattern of disease up to the age of 7 years, and 18.7% had symptoms every year up to the age of 7 years (*n* = 192). There was no difference in prognosis between children who first developed atopic eczema in the first and second years of life. Children who reported frequent scratching before the age of 2 years were more likely to have a poor prognosis and still have atopic eczema at the age of 7 years (cumulative OR 5.86, 95% CI 3.04 to 11.29).[134] [EL = 3]

Frequency, location and extent of flares

Atopic eczema typically has an intermittent pattern of flares which may occur rapidly and usually last from a few days to several weeks. Flares tend to recur in the same sites within individuals.[115] The frequency of flares is described in Section 7.7.

No UK data were found regarding the anatomical areas affected with atopic eczema in children. A study of children aged up to 10 years in Japan found a change in distribution of atopic eczema in children between the age of 1 and 2 years from the head, scalp and around the ears to the neck and flexures. The trunk was the most commonly affected area at all ages (*n* = 1012).[115,135]

A study in Nigeria found that atopic eczema was more often located in extensor areas in children aged 0–3 years, whereas in children aged 3–18 years atopic eczema was more often seen in

flexural areas (*n* = 1019, aged 4 weeks to 57 years).[136] [EL = 3] A study in Kenya found that initial presentation of atopic eczema in children aged 0–12 years at the time of examination involved facial or extensor sites in 86% of children. Although this pattern continued into later childhood, flexural involvement was more common in children older than 1 year compared with those aged less than 1 year (73% versus 37.5%).[137] [EL = 3]

Associations with asthma, hay fever and food allergies

One of the reviews found seven studies that investigated the development of asthma and/or hay fever (allergic rhinitis) in children with atopic eczema.[115] Concurrent or subsequent asthma was present in 10–53% (median 28%) and hay fever in 12–78% (median 59%). One study reported that more children with atopic eczema who attended as inpatients for their condition subsequently developed asthma (39%) compared with 22% of those treated only as outpatients (age 24–44 years at the time of follow-up). A confounding factor was that atopic eczema was more likely to be severe in children attending a hospital clinic, which is in itself a risk factor for the subsequent development of asthma. The review also reported that none of the studies set out to examine the association between asthma and atopic eczema and that few studies used clear definitions for asthma.[115] [EL = 3]

Three further surveys investigated the prevalence of asthma in children with atopic eczema in the UK. [EL = 3] They reported the following:

- 43% of children aged 5–10 years from general practice with atopic eczema had asthma, 45% had hay fever and 64% had asthma and/or hay fever (*n* = 137); atopic eczema was more likely to be severe in children with asthma (adjusted OR 2.0, 95% CI 1.1 to 3.6) or hay fever (adjusted OR 2.42, 95% CI 1.39 to 4.2)[133]
- 38% of children aged 3–11 years also had asthma at some time point (*n* = 1077)[122]
- the asthma prevalence was 17% in children with atopic eczema who were aged 0–2 years, increasing to 39% in those aged 3–7 years, and 42% in those aged 8–15 years (*n* = 429).[95]

One observational study in Sweden reported that 3.1% of children aged 1–2 years with atopic eczema also had hay fever (allergic rhinoconjunctivitis). The condition was more common in children with atopic eczema than in those without (12.3% versus 5.2%, 'ratio adjusted for heredity' 2.25, 95% CI 1.77 to 2.85).[138] [EL = 3]

The German multicentre atopy study (MAS)[139-141] reported that the lifetime prevalence of asthma was 10% at 1 year of age and 15% at 2 years of age (*n* = 1314).[139] The risk of having allergic airway disease (asthma and/or hay fever) at 5 years of age was higher (but not significantly so) in children who developed atopic eczema in the first 3 months of life.[141]

Food allergy

Several tests can be used to investigate whether a child is sensitised to foods, including skin prick tests and specific immunoglobulin E (IgE) measurements. However, the double-blind placebo-controlled food challenge (DBPCFC) is the gold standard for diagnosing food allergy in children. (The details of these and other tests and the proportions of positive reactions to food challenges in children in whom food allergy is being investigated are described in Chapter 6). No UK data were identified regarding food allergy or sensitisation in children with atopic eczema.

One study evaluated the prevalence of IgE-mediated reaction to foods in children and adults (aged 0.4–19.4 years, median age 2.8 years) with moderate to severe atopic eczema (mean SCORAD score 43) who were referred to a dermatologist. Overall, 65% had raised IgE levels (more than 0.7 ku/l) to at least one of six foods (milk, egg, peanut, wheat, soya and fish).[143] [EL = 3]

In infants aged 1 year (the Melbourne birth cohort) who were identified as being at risk of atopic disease, the prevalence of atopic eczema was 28.9%. The prevalence of IgE-mediated food allergy (wheal diameter of skin prick test at least twice that of the positive control (histamine)) was significantly higher in those with atopic eczema than those without (35% versus 12%, relative risk (RR) of atopic eczema because of IgE-mediated food allergy 3.1, 95% CI 2.1 to 4.4). The prevalence of IgE-mediated food allergy also increased with increasing severity.[144] [EL = 3]

Changes in sensitisation with age

Several studies have shown how sensitisation to various allergens changes with age. A short report comparing children with atopic eczema who were aged 2–4 years with those aged 10–12 years (n = 22) noted that sensitisation to food allergens (egg white, cow's milk, cod, wheat, peanut and soya) decreased with age, whereas sensitisation to common inhalant allergens (including house dust mite, grass, and tree pollen) increased with age.[145] [EL = 3] Another case series found a significant association between sensitisation to food allergens and atopic eczema in children aged under 2 years, which did not remain significant above this age. Conversely, the association between inhalant allergens (house dust mite and cockroach) increased with age, becoming statistically significant after the age of 5 years (n = 262).[146] [EL = 3]

The German MAS study[139-141] reported that the lifetime prevalence of food intolerance was 3% at 1 year of age and 4.5% at 2 years of age. Sensitisation (to one of nine allergens; IgE level of 0.35 ku/l or more) was 16% at 1 year and 24% at 2 years (n = 1314).[139] At 5 years, the proportion sensitised to inhalant allergens was higher than that sensitised to food allergens (28% versus 22.3%).[141] The odds of having sensitisation to inhalant allergens was significantly higher in children who had developed atopic eczema in the first 3 months of life.[141] In a subgroup of this population in whom complete specific IgE data were obtained, IgE levels specific to inhalant allergens were significantly higher than IgE levels specific to food allergens in children of the same age from the age of 3 years, $P < 0.006$ (n = 216). The proportion of children with atopic eczema in this subgroup was not stated.[140]

A Danish cohort study (n = 553) looking at sensitisation patterns in infants identified 61 children who had ever been diagnosed with atopic eczema between 3 and 18 months of age.[147] [EL = 2−] Children sensitised to at least one allergen were more likely to have atopic eczema than those who were sensitised to no allergens. Odds ratios depended on the measurement technique used (skin prick test, histamine release or IgE). Persistent sensitisation was also associated with atopic eczema when measured by skin prick test or specific IgE, but not by histamine release. Confidence intervals were wide.

Sensitisation and severity of atopic eczema

The level of sensitisation to cow's milk and egg was measured in the placebo arm of the Early Treatment of the Atopic Child (ETAC) study (an RCT comparing the antihistamine cetirizine with placebo) over the 18 month follow-up period. Sensitisation was defined as a specific IgE level of 0.35 ku/l or more (n = 382). The correlation between specific IgE levels and the severity of atopic eczema (SCORAD) was statistically significant for egg at all time points (months 0, 3, 12 and 18) and for cow's milk at months 0, 12 and 18).[148] [EL = 3] In a case–control study, 27% of children with atopic eczema (cases) had a positive skin prick test result for common food allergens (cow's milk, egg, cod, soya, peanut and wheat), and 15% a positive test result to IgE (no further details reported). Although no data were reported, it was noted that there was no significant difference in objective SCORAD scores in sensitised and non-sensitised cases with ongoing atopic eczema (n = 320).[149] [EL = 2−]

A smaller case series reported that 64% of children (mean age 3.5 years) had positive skin prick test results for food and/or inhalant allergens (n = 50). A significant association between sensitisation and severity (SASSAD score) was also reported.[150] [EL = 3]

Evidence statement for epidemiology

There has been little consistency among epidemiological studies of atopic eczema in children with regard to the populations studied or the methods used, leading to wide variations in the results reported in individual studies. It is not possible to give a definitive prevalence of atopic eczema. Prevalence may vary according to geographical location within the UK, but it is not clear whether it is location *per se* or other factors that influence the differences in prevalence figures. There are too few data on prevalence in different ethnic groups to allow conclusions to be drawn. Studies conducted in the UK over the past 30 years have shown a four-fold increase in the point prevalence of atopic eczema in children. Studies conducted in other countries in the 1980s and 1990s have also shown an increase in prevalence. [EL = 3]

In the majority of children, atopic eczema develops before the age of 4 years. In infants, atopic eczema commonly affects cheeks and extensor surfaces rather than flexural areas. [EL = 3]

Observational studies have shown that the majority of cases of atopic eczema are mild in severity. There is a lack of data relating severity of atopic eczema to age. There is some evidence that eczema is more likely to be severe in children who also have asthma, and in those with early onset of atopic eczema. [EL = 3] It is not clear whether prognosis is better in children with mild disease. [EL = 4]

The available data suggest that atopic eczema clears in most children by the teenage years and early adulthood, although relapses may occur. [EL = 3]

Atopic eczema is more likely to be severe in children who also have asthma or hay fever (one study). Varying prevalence rates for concurrent asthma and hay fever have been reported. The proportion of children sensitised to foods and inhalant allergens varies across studies. However, studies consistently show that sensitisation to foods decreases with age whereas sensitisation to inhalant allergens increases from the age of about 3–5 years. [EL = 3]

Cost-effectiveness

No cost-effectiveness issues could be addressed in relation to the epidemiology of atopic eczema because the use of healthcare resources was not the focus of the clinical question.

From evidence to recommendations

The GDG believes that it is important to provide information for children with atopic eczema and their parents/carers on the prognosis of the disease and possible associations between atopic eczema and other atopic diseases.

Recommendations for epidemiology

Healthcare professionals should inform children with atopic eczema and their parents or carers that the condition often improves with time, but that not all children will grow out of atopic eczema and it may get worse in teenage or adult life.

Healthcare professionals should inform children with atopic eczema and their parents or carers that children with atopic eczema can often develop asthma and/or allergic rhinitis and that sometimes food allergy is associated with atopic eczema, particularly in very young children.

There were no research recommendations on epidemiology.

6 Identification and management of trigger factors

The issues considered in this chapter are potential triggers for atopic eczema in children, clinical methods for identifying trigger factors that exacerbate established atopic eczema in children, and the evidence in relation to avoidance or elimination of potential triggers as part of the management of established atopic eczema in children.

6.1 Potential trigger factors

Studies considered in this chapter

Several reviews have documented factors that are believed to trigger atopic eczema. Trigger factors noted in the reviews are listed here.

Overview of available evidence

Many different factors have been proposed as triggers for atopic eczema in children, mainly as a result of epidemiological studies in which exposure to one or more of the factors has been shown to be associated with increased incidence of atopic eczema and/or exacerbation of established atopic eczema. Potential trigger factors include the following.[114,151-159]

- irritants – wool or synthetic clothing, soaps, detergents, perspiration, disinfectants and topical antimicrobials, and many chemical reagents
- contact allergens – preservatives in topical medications, perfume-based products, metals and latex
- foods/dietary factors – cow's milk, eggs, peanuts, tree nuts, wheat, soya, fish, shellfish and (rarely) others such as sesame, kiwi and legumes
- inhalant allergens (aero-allergens) – house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), animal dander, cockroach, tree and grass pollens, and moulds
- microbial colonisation and/or infection – *Staphylococcus aureus*, streptococcus species, *Candida albicans*, *Pityrosporum* yeasts, herpes simplex (colonisation and infection associated with atopic eczema in children is considered separately in Section 7.6)
- climate – extremes of temperature and humidity, and seasonal variation in the pattern of atopic eczema
- environmental factors – hard water, cooking with gas, proximity to road traffic, and environmental tobacco smoke
- familial factors – genetics, family size and sibling order
- social class (higher incidence in more affluent social classes)
- concurrent illness and disruption to family life – teething, psychological stress and lack of sleep.

While most triggers lead to reactions confined to the skin, allergic triggers are capable of inducing both skin and systemic responses. These responses are largely mediated via IgE and T cell responses causing immediate (type 1) and/or delayed (late-phase or type 4) allergic reactions. Immediate reactions in the skin can lead to erythema and itching, the onset of urticaria (hives) and/or angioedema (swelling) resulting in an acute flare of atopic eczema. These reactions may be accompanied by systemic features involving the gut (oral pruritus, vomiting, diarrhoea and/or abdominal pain), the respiratory tract (rhinitis, wheeze, cough and stridor (difficulty breathing)) or

the cardiovascular system (drop in blood pressure and/or collapse). The involvement of breathing difficulties or a drop in blood pressure constitutes an anaphylactic reaction. Delayed reactions in the skin cause itching and flares of atopic eczema and they may be accompanied by symptoms in the gut (vomiting and/or diarrhoea).

6.2 Identification of trigger factors

Studies considered in this section

Studies evaluating the accuracy of challenge tests (skin tests (skin prick tests and atopy patch tests), IgE tests and skin application food tests (SAFTs)) for the identification of trigger factors for atopic eczema were considered for this section. Skin prick (or puncture) tests are used to detect skin responses to material (for example, foods or inhalant allergens) applied directly to the skin; the responses are usually evaluated over a short period of time (15–20 minutes). The presence of antigen-specific IgE produces a wheal and flare response. The atopy patch test is a skin test where whole food proteins are applied to the skin under occlusion for 24 hours. The test site is evaluated at the time of removal and 48 hours later for evidence of inflammation that can be scored by severity. Controls are applied to determine possible irritant reactions. Raised IgE levels in the blood are an indication of allergy. Other forms of patch tests are used to diagnose contact allergies: the diagnosis and management of contact allergy is outside the scope of this guideline, although such allergies may occur in association with atopic eczema (for example, when a child with atopic eczema develops an irritant reaction or allergy to a topical treatment; see Chapter 7).

Overview of available evidence

No studies have considered the accuracy of any tests for diagnosing inhalant allergies. No tests exist for investigating reactions to climatic, psychological or environmental trigger factors.

Nineteen studies have considered the diagnostic accuracy of one or more tests (skin prick test, atopy patch test, SAFT and/or specific IgE) for detecting food allergy in children with atopic eczema. The double-blind placebo-controlled food challenge (DBPCFC) test is considered to be the gold standard for the diagnosis of food hypersensitivity.[160] The reference standard against which the tests were compared was a DBPCFC in eight studies (total *n* = 787),[161-170] and an open food challenge in ten studies (total *n* = 891).[171-180] A further study (n = 437) was designed to use the DBPCFC, but open food challenges were used in children younger than 1 year with a history of immediate reactions.[181] A further 11 studies considered how diagnostic accuracy might change when tests were undertaken in different ways, such as using different foods or changing the thresholds for what constituted a positive test. The findings of these studies are described briefly below; more detailed descriptions for each study are presented in Appendix C. Note that some studies were described in more than one publication.

Nine studies present the outcome of food challenge tests.

Identifying food allergy in children with atopic eczema

The studies were heterogeneous in terms of the age of the population evaluated, whether single or multiple tests were evaluated, and in how the tests were undertaken (including variation in the foods tested and which preparation of a particular food was used).

In most of the studies, the age of the population was within the range of 2 months to 12 years. However, older children and adults were included in some studies (up to the age of 28 years).

The foods investigated were predominantly cow's milk and/or egg, and also wheat, soya, fish and peanuts. Some studies considered diagnostic accuracy for one food only, while other considered accuracy for a range of foods. There was also variation in whether studies reported the diagnostic accuracy for an immediate reaction (usually occurring within 2 hours), a delayed reaction (occurring within 2–72 hours), or any reaction (immediate or delayed, combined). When considering whether a food allergen triggers atopic eczema, delayed reactions are more relevant. Only the minority of studies considered delayed reactions.

The studies were generally consistent in the definition of a positive test (erythema usually with infiltration for an atopy patch test, and a minimum wheal size of 3 mm in diameter on skin prick test). However, while the specific IgE level indicative of a positive test was 0.35 ku/l in all DBPCFC studies, there was greater variability in the level compared with an open challenge (ranging from 0.35 to 99 ku/l).

While all studies that used open challenges were considered to be of poor quality, [EL = DS III] some of the DBPCFC tests were of better quality.[162–164,166] [EL = DS II] In most studies it was not clear whether the challenge testing was undertaken blind to (without knowledge of) the results of the tests being evaluated. Neither was it explicitly stated in several studies whether the population evaluated had atopic eczema that was suspected to be exacerbated by food allergy.

As indicated above, because there was heterogeneity in the design of the individual studies, interpretation of the results was difficult. Sensitivity and specificity values were focused on for the main guideline text (although other values such as PPVs and NPVs are reported in Appendix C) as these parameters reflect the performance of the tests, and do not vary with prevalence (unlike predictive values).

Overall summaries of the sensitivity and specificity of the tests for diagnosing reactions to foods (across all studies) are presented below. However, it should be noted that some of these data represent results from only one study.

Atopy patch test
Compared with the DBPCFC test, the atopy patch test (erythema usually with infiltration) had high specificity (81–96%) for any reaction (immediate, delayed, or immediate and delayed combined) to cow's milk, egg and soya. Specificity for any reaction to wheat was more variable (35–94%). Compared with an open food challenge, the specificity results for any reaction were more variable for cow's milk, egg, wheat and peanut. Compared with DBPCFC or an open food challenge, sensitivity results for any reaction to a single food (cow's milk, egg, wheat, soya and peanut) were more variable. Sensitivity and specificity results compared with DBPCFC were both more variable when considered for several foods together (no data compared with an open food challenge).

Skin prick test
Compared with the DBPCFC test the skin prick test (wheal size 3 mm or greater) had high sensitivity (90–95%) for diagnosing an immediate response to fish and peanut, or to several foods together (results from one study); specificity results for these foods were more variable. The sensitivity and specificity for detecting any reaction (immediate, delayed, or combined and compared with DBPCFC) to all other allergens tested (cow's milk, wheat and soya) were more wide-ranging across studies. Compared with an open food challenge, sensitivity and specificity results for any reaction (immediate, delayed, or combined) to all allergens were also more variable.

Specific IgE
The sensitivity of specific IgE (more than 0.35 ku/l) for detecting any reaction (immediate, delayed, or combined) to cow's milk and egg was high (83–100%) compared with the DBPCFC test. Sensitivity for detecting an immediate reaction to wheat, soya, fish and peanut compared with DBPCFC was also high (94–97%; one study only). Sensitivity for a combined immediate and delayed reaction to wheat or soya was more variable (no data for delayed reactions). Specificity results for each of the allergens alone or when considered together were more variable. Compared with an open food challenge, both sensitivity and specificity results were less consistent across all foods tested. The specific IgE level indicative of a positive test ranged from 0.35–99 ku/l in the open challenge studies.

Effect of changing test parameters
The available data for each type of test do not show consistency in sensitivity or specificity results. This might reflect the way the particular tests were undertaken or the criteria used to define positive test results. Several studies have considered whether changing certain parameters of a test affects their diagnostic accuracy in children with atopic eczema.[165,167,175,182–191] The accuracy of the atopy patch test varied according to the size of the chamber used for occlusion, the vehicle and concentration used to apply the allergen to the skin, and according to which skin sign was

taken to indicate a positive test. [EL = 3/EL = DS III] There was some evidence that increasing the wheal size that constituted a positive test on skin prick testing increased the specificity of the test. The specific IgE levels that gave PPVs of 95% for certain allergens were estimated in one study. [EL = DS III]

Outcome of challenge tests

One study recruited 63 children (age range 0.4–19.4 years) with persistent atopic eczema from a dermatology clinic. After screening for food allergy, 19 children underwent DBPCFC. There were four positive challenges to egg, three to milk, three to wheat, two to barley and one to beef. Thirty-seven percent of children in this study were diagnosed with food allergy based on double-blind and open challenges and convincing histories of reactions to foods.[143]

Three studies conducted in a single clinic reviewed patient records of consecutive referrals for food allergy investigation in children with atopic eczema. In the first study, 107 children (age range 5 months to 12 years, median age 21 months) underwent DBPCFC. Eighty-seven children (81%) showed reactions to at least one food. Early skin reactions were mainly caused by egg and cow's milk, with wheat and soya producing a small number of reactions. Isolated late reactions were produced by all four allergens in 25% of the total number of reactions.[166]

The second study reviewed 139 children (age range 2 months to 11.2 years, median age 13 months). DBPCFC was conducted in all children and, of 208 challenges, 111 were positive. Positive challenges were due to cow's milk (47%), egg (34%) and wheat (19%). It is not clear how many children had at least one positive test. Immediate and late reactions were observed.[547]

There were 98 children in the third study (age range 2 months to 11.2 years, median age 13 months). Of 173 challenges, 55% were positive, including 45/71 positive challenges to cow's milk, 28/42 to egg, 18/35 to wheat and 4/25 to soya. It is not clear how many children had at least one positive result. All late reactions (25% of the total) were skin related.[165]

In one small study, 26 children (age range 16 months to 19 years, median age 11 years) with atopic eczema, elevated IgE level), suspected food allergy and ability to cooperate with food challenge procedures were subjected to DBPCFC. Fifteen children had positive reactions to at least one food. Foods provoking cutaneous reactions were wheat, soya, milk, egg, rye, chocolate and chicken.[548]

A later study by the same group investigated 113 people (age range 4 months to 24.5 years, median age 6 years) with severe atopic eczema for food allergy. Three hundred and seventy DBPCFCs were undertaken, of which 101 were positive in 56% of patients. Major allergens in this study were egg and peanut, with 85 challenges provoking skin reactions. Allergens provoking a small number (fewer than 6) of reactions were milk, soya, wheat, fish, chicken, pork, beef and potato.[549]

In another study, food allergy was identified by DBPCFC in 39% (n = 165) of patients (age range 4 months to 21.9 years, mean age 49 months) with atopic eczema attending a specialist allergy clinic. The main foods provoking positive challenges within 2 hours were peanut (n = 27), egg (n = 33) and milk (n = 14). No delayed reactions were observed.[550]

Sixty-four children (age range 1–10 years, median age 2 years) with atopic eczema and suspected food allergy were investigated in this study. There were 106 DBPCFCs, of which 46% were positive. The allergens tested were cow's milk, egg, wheat and soya. All of the isolated late reactions (12% of total) were eczematous.[169]

Seventy-four children (age range 6 months to 16.3 years, median age 2.5 years) with atopic eczema who had been referred to paediatric dermatology or allergy clinics were enrolled for evaluation of food allergy. Six children underwent DBPCFC and positive reactions were to milk (three challenges) and wheat (two challenges).[142]

6.3 Management of trigger factors

Studies considered in this section

For this section, RCTs evaluating the effectiveness of trigger factor management strategies in children with atopic eczema were considered where available. Where RCTs were not available, studies of any design were considered.

The management of trigger factors in atopic eczema was considered in three systematic reviews.[26,156,192] Because two of the reviews included children and adults,[26,156] and because of overlap in the studies included in reviews, studies including the population of relevance to this guideline are reported individually here, together with other evidence identified.

Overview of available evidence

The evidence identified in relation to managing trigger factors consisted broadly of exclusion diets and inhalant-allergen avoidance strategies (predominantly avoidance of house dust mite). Various diets have been evaluated, including exclusion of cow's milk and/or egg, the use of restrictive diets ranging from elemental diets (consisting of products containing amino acids only) to diets including up to 20 foods. Sodium cromoglicate has been evaluated in comparison with, and in addition to, dietary interventions. Probiotics have been evaluated as an adjunct to milk substitutes, and vitamin E and zinc as treatments for atopic eczema.

No evidence was identified regarding avoidance or elimination of the following factors: skin irritants, extremes of temperature or humidity, and stress.

Cow's milk and egg exclusion diets

Two double-blind randomised crossover trials of egg and cow's milk exclusion diets involved children with atopic eczema.[193,194] [EL = 1−] The studies had 4 or 6 week treatment periods, with a washout period of the same duration in-between. As well as eliminating eggs and cow's milk, chicken and beef were eliminated, and a soya-based milk substitute given; the control group received a preparation containing a mixture of dried eggs and cow's milk as a milk substitute. Neither study stated whether there was clear evidence of allergy or intolerance to the eliminated foods, although it was reported in one that three of the 20 children who completed the study had a history of exacerbation of skin symptoms following ingestion of eggs or cow's milk.[193] The most common reason for withdrawal from both studies was non-adherence to the diet. Both studies analysed results only for those who completed treatment.

The first RCT (n = 36; 56% completed), in children aged 2–8 years, found significantly greater improvements in the diet group versus control in atopic eczema activity (global improvement) and skin area affected, sleeplessness and antihistamine usage, with no significant difference between diet and control groups in pruritus (mean improvement 4.49, standard error 2.25).[193] The response in the diet group was significantly greater during the first treatment period than the second treatment period for activity, area and sleeplessness, but there was no significant difference between the first and second treatment periods for pruritus or antihistamine usage. For pruritus and sleeplessness this 'order' effect was greater than the difference between diet and control groups. It was also reported that there was no correlation between positive prick test to the egg and cow's milk antigens and response to diet, but no data were reported.[193]

The second RCT, in children and adults aged 1–23 years, found no significant differences between elimination and control diets in area (mean −1, 95% CI −6 to 3.4) or itch (mean 15, 95% CI −21 to 51) scores. Use of topical corticosteroids was higher during the elimination diet (n = 53; 40 completed).[194]

Two case series also reported the effects of egg and/or cow's milk exclusion diets in children with atopic eczema.[195,196] One series eliminated cow's milk and egg from the diet of children (aged 0.4–15 years) for 3 weeks (n = 91; 73% completed and analysed). Improvements in severity scores were reported at endpoint.[196] In the other series, children aged 2–14 years who had not responded to usual treatments eliminated cow's milk and egg, or cow's milk only, from their diet for 4 weeks. The decision on whether to exclude milk alone or both foods was dependent on which was suspected of precipitating the atopic eczema. However, the outcome was only

reported as cure or improvement, with no definition of either term. Additionally it was not clear how many of the children eliminated only milk or both foods from their diet (*n* = 59).[195] [EL = 3]

One case series of children with atopic eczema (*n* = 11, median age 4 years) documented acute allergic reactions to cow's milk after prolonged cow's milk elimination diets.[197] [EL = 3]

Egg exclusion diets

Two controlled trials considered the effects of egg exclusion on atopic eczema in infants.[198,199] The first was a double-blind RCT in which all the infants had a raised IgE to egg on a radioallergosorbent test (RAST), and the majority also had a positive test on a DBPCFC test (*n* = 62; 89% analysed).[198] The control group were not given any specific dietary advice. After 4 weeks' intervention, the reduction in body surface area affected was significantly greater in the diet group compared with control (mean difference 5.25%, 95% CI 0.1% to 10.9%, *P* = 0.04). Differences between groups in severity scores were not significant (6.1, 95% CI −0.1 to 12.3, *P* = 0.05), although there were some discrepancies in the trial report between data presented in the text and in the abstract.[198] [EL = 1−]

The second trial, described as a single-blind controlled study, reported the proportions of children in four age categories whose condition was 'better' after 2 weeks' treatment. However, 'better' was not defined (*n* = 213; 65% of whom completed treatment and were analysed).This study was not considered further.[199] [EL = 1−]

Cow's milk substitutes

One RCT compared two milk substitutes in infants with atopic eczema and allergy to cow's milk (shown on DBPCFC; *n* = 73).[200] An amino acid-based formula was compared with a hydrolysed whey formula. Energy intake was similar in both groups. A significant improvement in the SCORAD severity index was seen overall, from a mean of 24.6 at entry to 10.7 after 6 months (*P* < 0.0001); data were not reported separately by treatment group. In the amino acid group there was a significant increase in the length standard deviation score (SDS) from baseline (*P* < 0.04), while there was no statistically significant change in the hydrolysed whey group. Weight-for-length values were 'stable' in both groups.[200] [EL = 1−]

In a randomised study infants with atopic eczema and proven allergy to cow's milk (on double-blind food challenge) were given hydrolysed whey or amino acid formulas as milk substitutes (*n* = 45).[201] Although the study was described as randomised in the abstract, randomisation was not mentioned elsewhere in the paper. Other dietary restrictions (egg and cereals) were also used in two-thirds of infants. At 8 months, SCORAD scores had improved significantly from baseline in those receiving either milk substitute. The statistical significance of changes in weight and length of infants was also reported, although the data were only presented in graphs. The graphs showed that weight and length increased in both groups in the first month of treatment, and they 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 and length at 9 months appeared to be the same or worse than at baseline. There was overlap of the 95% CIs for the groups for weight indicating that the difference between the groups was not statistically significant for this outcome. However, the difference between groups for length was statistically significant.[201] [EL = 1−]

Milk substitutes for women who are breastfeeding

One double-blind crossover RCT considered the effects of an exclusion diet plus a milk substitute in mothers of breastfed infants with atopic eczema (*n* = 19; 17 completed and analysed; aged 6 weeks to 6 months).[202] [EL = 1−] This was the only study relevant to the guideline clinical question in a review of maternal dietary antigen avoidance during pregnancy and/or lactation.[203] The foods excluded from the mothers' diet were cow's milk, egg, chocolate, wheat, nuts, fish, beef, chicken, citrus fruits, colourings and preservatives. The milk substitutes taken were a preparation containing soya and one containing cow's milk and egg powder. Area and activity scores (the latter a measure of the severity of the condition on 20 body surface areas) fell from baseline with both milk substitutes after 4 weeks' use. The difference between groups was not statistically significant (activity score, exclusion diet plus soya versus exclusion diet plus cow's milk and egg, 104 versus 12.6, *P* value not reported; area score, exclusion diet plus soya versus exclusion diet plus cow's milk and egg, 9.0 versus 8.9, *P* value not reported). A subsequent open, uncontrolled study was undertaken in the same group because of concerns that the soya preparation may have

triggered symptoms in the first study (*n* = 18). In this open study, mothers took their usual diet (containing cow's milk and egg) for 2 weeks, followed by an exclusion diet for 2 weeks (the same as that taken during the first study), then the usual diet repeated for 2 weeks. Activity and area scores fell significantly after the exclusion diet (at week 4), and remained at around this level after the reintroduction of the usual diet (week 6).[202]

Restrictive diets

Three studies considered the effects of restricting foods consumed by children with atopic eczema (two case series and one controlled study).[204-206] The first case series considered a 2 week diet consisting of up to 19 foods (including meats, carrots, lettuce, parsley, pears, rice, plain flour, sugar, golden syrup, honey, oils, vinegar, salt and pepper and coffee; *n* = 29, age range 2–12 years).[204] The withdrawal rate was 55%, and half of the withdrawals were because the diet was considered to be too restrictive. Thirteen children were evaluated at the end of the 2 week diet. According to the parents' global assessment seven were improved, three remained the same and three deteriorated. Based on the dermatologist's assessment of inflammation, lichenification, and cracking, five were improved, seven remained the same and one deteriorated.[204] [EL = 3]

The second case series included children aged 10 months to 4 years with severe atopic eczema that persisted despite usual treatment and elimination of the food items to which the child was suspected to be allergic (*n* = 13).[206] A diet consisting of the following foods was taken for 1 month: casein hydrolysate, lamb, rice, corn, corn oil, potato, cucumber, melon, bilberries, salt, sugar, and gluten- and milk-free bread. The numbers of children whose condition improved according to investigator's and parents' scores of the severity of the condition were six and eight, respectively. Not all the children who improved according to the investigator improved according to the parents.[206] [EL = 3]

The controlled study reported changes in IgE and peripheral blood mononuclear cell concentrations following elimination diets (eliminating the 'offending foods') in children aged 3 months to 13 years (*n* = 153). Changes in severity from baseline were also reported, but a lack of between-group analysis and of details of the diets given made interpretation difficult.[205] [EL = 2−]

Few foods diets

Three studies considered the effectiveness of 'few foods' diets (eliminating all but five to eight foods); these were a single-blind RCT and two case series.[207-211] The single-blind RCT evaluated a diet (including either whey or casein hydrolysate milk formula) in children aged 0.3–13 years with atopic eczema that persisted despite conventional treatment (*n* = 85).[207] After 6 weeks there were no significant differences between the diet group and control group (continued usual diet) in changes in any outcome (body surface area affected, severity, daytime itch, or sleep disturbance). The withdrawal rates were 59% in the diet group (the most common reason for withdrawal being non-adherence), and 15% in the control group; only results for those who completed the 6 week intervention period were analysed.[207] [EL = 1−]

A case series of children with extensive atopic eczema (affecting 30% or more of body surface area) that responded poorly to conventional treatment or who had a history of food intolerance were given a few (six) foods diet (*n* = 63, age range 0.4–14.8 years).[208,210] After 6 weeks, the median severity score fell by 33%, with 52% having a 20% or greater reduction in score. 'Little or no benefit' was seen in 39%. The withdrawal rate was 14%. Of the 68% who were followed up for 1 year, the outcome was similar in children regardless of their response to the 6 week few foods diet, although no data were presented.[208] Some children from this study were subsequently given an elemental diet (see below).[209,210] [EL = 3]

Another case series of children with severe atopic eczema evaluated a few foods diet (*n* = 66, age range 0.6–17 years).[211] Twenty-four patients (36%) were reported to have 'worthwhile' improvement (the term 'worthwhile' was not defined) from the diet (median duration 26 days, range 19–44 days). In 15 of these (23% of the total group), improvement persisted on dietary treatment, but three withdrew because the diet was too burdensome. Overall, 12 (18%) persisted with the diet and had continued benefit over the duration of follow-up (mean 48 weeks, range 26–71 weeks). The outcomes beyond this follow-up period were not reported.[211] [EL = 3]

Elemental diets

A randomised crossover study in infants and children with a positive skin prick test and raised cow's milk-specific and soya bean-specific IgE evaluated an amino acid-based elemental diet (*n* = 15; 11 analysed).[212] Dairy- or soya-based products were also excluded from the diet. The control group continued with a pre-existing formula (no further details were reported). Following 6 weeks' treatment, there were no significant differences between the amino acid-based elemental diet and the control diet in SCORAD scores or in global health scores. A significant treatment-by-period interaction was reported for SCORAD, which was greater than the between-group treatment difference.[212] [EL = 1−]

A case series of children aged 0.4–13 years with severe and extensive atopic eczema were hospitalised for treatment with an elemental formula only (the product contained 100% free amino acids). Pet and house dust mite avoidance measures in the children's homes were a prerequisite for treatment (*n* = 37).[209,210] After a median duration of 30 days' treatment, 27% were considered to be 'treatment failures' because their severity scores were unchanged or worse compared with baseline. In the 73% for whom treatment was considered to be successful, the severity scores decreased to 27% of the baseline score (range 3–67%; no further details of who had greatest or least benefit were presented). No significant differences in demographics or in clinical features were found between those in whom treatment was successful and those in whom it was not successful. Reported adverse effects were weight loss of up to 17% (in 30 of 34 evaluated), loose stools (19%), and a reduction in serum albumin in 93% of 27 children in whom this parameter was measured (from a mean of 30.8 g/l to a mean nadir of 21.2 g/l). No electrolyte disturbances were reported.[209,210] [EL = 3]

A further case series reported the outcomes of an elemental diet in children with atopic eczema (*n* = 10, age not specified).[213] Only the elemental diet was used for 2 weeks, followed by addition of pumpkin, potatoes, zucchini, apples, pears and pure vegetable margarine. Two children stopped using the diet after 1 week. In the other eight, the atopic eczema scores (a measure of severity, extent and of treatment required) fell significantly at 6 weeks, and increased again after reintroduction of their usual diet. Adverse effects were not considered. [EL = 3]

The effectiveness of a 'home-made meat-based formula' diet was considered in a case series of children with severe atopic eczema (*n* = 16, aged 5–24 months).[214] The children had positive skin prick test results to cow's milk, egg, and wheat and/or soya. The formula consisted of lamb, olive oil, rice flour and water, supplemented with calcium and vitamin D. After 1 month, the severity score had fallen (no statistical analysis reported), with no significant changes in lipid levels. It was reported that all the children had gained weight normally, but no data were presented.[214] [EL = 3]

Sugar exclusion

One study considered whether avoiding sugar had an impact on atopic eczema in children and adults (*n* = 30; 9 children).[215] No significant changes in SCORAD severity scores were seen in the children's atopic eczema 1 week after the elimination diet, and differences in SCORAD following a double-blind or placebo food challenge were also not significant. Aspartame was offered as a replacement for sugar, but it was not clear how many took this.[215] [EL = 3]

Sodium cromoglicate

Four studies evaluated the effectiveness of sodium cromoglicate therapy in children with atopic eczema, either compared with or in addition to an elimination diet (three RCTs and one case series).[216-219] The first RCT compared a restricted diet (consisting of 12 foods) with oral sodium cromoglicate in children aged 5 months to 14 years. After 4 weeks' treatment, there were no significant differences between groups in severity or disease extent (*n* = 1085, 80% analysed).[216] [EL = 1−]

Two placebo-controlled crossover RCTs evaluated the addition of sodium cromoglicate to an elimination diet tailored to individual children with atopic eczema.[217,219] In the first RCT, significant improvements in severity were reported for both groups after 6 weeks' treatment, but no between-group analysis was reported to allow comparison between groups (*n* = 29, 76% completed and analysed, aged 3–12 years).[217] [EL = 1−]

The second crossover RCT found no significant differences between investigators' or parents' assessments of severity at 8 weeks when treatment with sodium cromoglicate was followed by placebo. However, improvements in severity were significantly greater with sodium cromoglicate when the treatment sequence was reversed (that is, placebo taken first, *n* = 31, 94% analysed, aged 6 months to 10 years).[219] [EL = 1−]

In the case series, sodium cromoglicate was added to an individually tailored exclusion diet in children aged 1–15 years (*n* = 35). However, the outcome of sodium cromoglicate treatment was only expressed as 'improved' or clear/almost clear, with no definitions given. Without a control group the study was of limited value, and it was not considered further.[218]

Vitamin and mineral supplementation

Two placebo-controlled RCTs considered the effectiveness of zinc or vitamin E for atopic eczema.[220,221] The trial involving zinc included children aged 1–16 years who continued with their usual treatments for atopic eczema (emollients and topical corticosteroids). Itch scores were significantly higher in children treated with zinc than with placebo, otherwise there were no significant differences in any outcome at 8 weeks (sleep disturbance, redness, surface area or combined disease severity scores, or in use of other treatments; *n* = 50, 84% analysed).[220] [EL = 1−]

The trial of vitamin E included children and adults (*n* = 96, aged 10–60 years).[221] Treatment with emollients was continued. Vitamin E or placebo was given for 8 months, after which the global assessment of the condition (classifications not defined) found worsening in 8% of the vitamin E group versus 78% in the placebo group; no change in 12% versus 11%, slight improvement in 20% versus 9%, great improvement in 46% versus 2%, and almost complete remission in 14% versus 0%. No statistical analysis of the data was presented and no adverse effects were reported.[221] [EL = 1−]

Probiotics

Three double-blind RCTs considered the effectiveness of a milk substitute supplemented with probiotics for the treatment of atopic eczema in infants with suspected cow's milk allergy.[222-224] The cow's milk substitute in all three studies was a hydrolysed whey formula, with *Lactobacillus* added in the intervention group. Two studies had an additional intervention group: one received a mixture of probiotics (*Lactobacillus*, *Bifidobacterium*, *Propionibacterium*) and the other received *Lactobacillus rhamnosus*. Control groups received the hydrolysed whey formula only. Two studies evaluated 1 month's use. Of these, the study with three treatment arms found no significant differences between the groups treated with probiotics and the control group in changes in SCORAD severity scores (*n* = 252, 91% completed and analysed).[222] [EL = 1−] The second study reported significant improvements in SCORAD scores from baseline in the group receiving the hydrolysate plus probiotic. However, no between-group analysis was reported (*n* = 31).[223] [EL = 1−] The treatment period in the remaining study was 3 months and no differences in SCORAD reduction were found between the three groups.[224] [EL = 1−]

House dust mite avoidance

Two RCTs in children[225,226] and one involving children and adults[227] considered the effectiveness of house dust mite avoidance. One of the RCTs evaluated the effects of bedding encasement with microfine fibres on mite sensitisation in children with atopic eczema, but did not report any clinical outcomes (only IgE and house dust mite levels were measured) and is therefore not considered further (*n* = 57).[225]

A 2 month placebo-controlled RCT in young children (aged 2–10 years, mean 3.9 years) evaluated house dust mite allergen avoidance measures. The children had moderate atopic eczema (SCORAD 27–33) associated with high total and/or specific IgE serum levels (*n* = 41).[226] The mite avoidance measures consisted of encasing mattresses and pillows, a hot weekly wash of bedding, vacuuming of living rooms and bedrooms at least twice a week, and removing or washing soft toys once a week; pets were not allowed. In the control group the previous house cleaning strategy was continued. After 2 months' intervention, a significant reduction in the SCORAD index was reported in the avoidance group; the score also fell in the control group, but no between-group analysis was reported. Significant reductions from baseline in dust load and house dust mite allergen concentrations were reported in the avoidance group, but not in the control group;

again no between-group analysis was reported, nor was there any consideration of whether groups were similar at baseline in the parameters measured.[226] [EL = 1−]

A further double-blind RCT (*n* = 60, aged 7–65 years) compared a house dust mite avoidance strategy (GORE-TEX® bedding system, carpet spraying and use of a high-filtration vacuum cleaner) with placebo in children and adults who had positive results in skin prick tests using a range of inhalant allergens. [227] After 6 months, the reduction in severity (measured using SASSAD) was significantly greater in the avoidance group compared with placebo (mean difference 4.2, 95% CI 1.7 to 6.7, *P* = 0.008; mean difference in final severity score in children (aged younger than 17 years) 11.1, 95% CI −3.1 to 25.3, *P* = 0.019). The reduction in bed mattress dust load was significantly greater in the intervention group compared with placebo (98% versus 16%, *P* = 0.002). Median reductions in the concentrations of the house dust mite allergen in bedroom or living room carpets were not significantly different between intervention and control groups (91% versus 89%, *P* = 0.94 and 76% versus 38%, *P* = 0.27, respectively).[227] [EL = 1−]

In a non-randomised controlled study, the effectiveness of an air cleaning system (in a 'clean-room') for the treatment of people aged 8–75 years with atopic eczema who had high specific IgE levels to house dust mite was evaluated (*n* = 30).[228] Participants were hospitalised for 3–4 weeks, and were exposed to either an air cleaning system in a clean-room, or to a similar room without the air cleaning system. The only clinical outcome reported was time to recurrence of symptoms – it was unclear whether this referred to all symptoms or specifically to itchiness. It was reported that time to recurrence of symptoms in those in the clean room who had high IgE to house dust mite was a mean of 8.4 months, whereas in those with no raised IgE to house dust mite the time to recurrence was 1.7 months. In the control group (no air filtration system, and high IgE to house dust mite) the time to recurrence was 1.6 months. No baseline data were reported.[228] [EL = 2−]

Hyposensitisation to house dust mite

Two studies considered the effects of hyposensitisation to house dust mite on atopic eczema in children who had a positive skin prick test result to this allergen. One was a double-blind RCT with 6 months' follow-up (*n* = 26),[229] [EL = 1−], and the second was a controlled trial of up to 3 years' duration (*n* = 60).[230] [EL = 2−] Neither study found significant differences in the severity or clinical features of atopic eczema between those receiving hyposensitisation therapy and those in the control groups (placebo or continued usual treatment).[229,230]

Evidence statement for identification and management of trigger factors

Potential trigger factors

A plethora of potential triggering factors for atopic eczema has been documented in the scientific literature, including irritants, contact allergens, food and dietary factors, inhalant allergens, microbial colonisation of skin, climate, environmental factors and familial factors. Many of these have been considered only in the context of primary causes/prevention of atopic eczema (which are outside the scope of this guideline), rather than in terms of triggering exacerbations of established atopic eczema. Most data in relation to the identification and management of trigger factors relate to testing for food allergies and elimination diets, and avoidance strategies for inhalant allergens.

Identification of trigger factors

There has been little consistency among the studies that have considered the accuracy of atopy patch tests, skin prick tests and specific IgE for identifying food allergy in children with atopic eczema. The studies varied in the age of the study populations, the foods tested, the standard against which results were compared (DBPCFC or open food challenge), and in the way the tests were undertaken (the types of foods used and the criteria used to define positive test results). There was evidence that changing the definition of a positive test result for the atopy patch test, the skin prick test and specific IgE changed the diagnostic accuracy of the tests. [EL = DS III]

Only a minority of studies focused on delayed reactions (in which the suspected food caused exacerbation of atopic eczema). The studies varied in whether they reported diagnostic accuracy of a test for a specific allergen or for all allergens together, and whether they considered accuracy for detecting immediate and/or delayed reactions.

The general trends for sensitivity and specificity of tests for diagnosing any reaction to foods across these studies were as follows:

- The atopy patch test (erythema usually with infiltration) had high (more than 80%) specificity for cow's milk, egg, soya and peanuts compared with DBPCFC or open food challenges. Specificity results for wheat and sensitivity results for all foods were more variable.
- The skin prick test (wheal size 3 mm or greater) had high sensitivity for egg, fish and peanut compared with DBPCFC; results for cow's milk, wheat and soya were variable. Sensitivity results compared with open challenge were more variable. Specificity results for all allergens were more variable.
- The sensitivity of specific IgE for cow's milk and egg was high compared with DBPCFC, but less consistent compared with open food challenge. Specificity results for wheat were more variable. Sensitivity results for all foods were more variable. The specific IgE level indicative of a positive test result was 0.35 ku/l in DBPCFC studies, but ranged from 0.35 to 99 ku/l in the open challenge studies.

Studies that reported the diagnostic accuracy of a test for any food allergen might have been useful for ruling out food allergy, but the available data did not show consistency in sensitivity or specificity results. [EL = DS III]

Outcome of challenge tests

Positive challenges were reported in 40–81% of oral food challenge tests. Egg, cow's milk and nuts were consistently identified as being the most frequent allergens to trigger an immediate response. Wheat, soya, fish and shellfish were also identified as additional food allergens triggering immediate or delayed responses.

Immediate reactions involved the skin, gut and respiratory systems. Skin reactions were reported as eczematous symptoms or urticaria. Late eczematous reactions occurred in 45% of challenges in two studies. One study reported only a delayed reaction (that is, no immediate response) in 12% of children.

The prevalence of food allergy in children with atopic eczema in secondary care settings was estimated to be 37–56%. [EL = 2]

Management of trigger factors

Most evidence regarding the management of trigger factors in children with atopic eczema related to dietary exclusions or house dust mite avoidance strategies. There was little consistency across studies in the type of diet evaluated, and indications for special diets were not always made clear. There were confounding factors in many studies, for example exclusion of other foods in addition to cow's milk and egg in studies specifically evaluating exclusion of cow's milk and egg.

In crossover RCTs, 4–6 weeks' cow's milk exclusion diets produced conflicting results with significant differences between treatment and control arms in some, but not all, outcomes. The most common reason for withdrawal from the studies was non-adherence to the diet. [EL = 1−] In infants with moderate to severe eczema and cow's milk allergy, those fed a whey formula did not exhibit a linear growth pattern during the 9 month follow-up period whereas those fed an amino acid formula did. [EL = 2−]

Egg exclusion alone in children with suspected egg allergy led to improvements in extent, but not severity, of atopic eczema (one RCT). [EL = 1−]

There was no good evidence to support the use of the following interventions in the management of children with atopic eczema: 'few foods' diets, elemental diets, addition of probiotics to milk substitutes, sodium cromoglicate (alone or in addition to restricted diets), or excluding foods from the diet of women who are breastfeeding. [EL = 1−]

There was some evidence that house dust mite avoidance strategies in children and adults led to greater improvements in atopic eczema severity than placebo after 2–6 months. [EL = 1−]

Cost-effectiveness

There was no published evidence on the cost-effectiveness of any of the tests for diagnosing trigger factors. A cost-effectiveness model to assess the comparative advantage of alternative

means of diagnosing trigger factors was not feasible owing to the complexity of the data required (which would require assessment of all the consequences of true and false positive and negative diagnoses of a range of trigger factors on the management and subsequent outcomes of atopic eczema in children) and was not identified as a priority for this guideline.

From evidence to recommendations

It is the GDG's view that a clinical assessment (clinical history and physical examination) should play a key role in identifying potential trigger factors, including suspected food allergy. The clinical pattern of atopic eczema can indicate potential allergies (particularly to inhalant allergens).

Food allergy plays an important role in triggering both immediate and delayed skin reactions in children with moderate or severe atopic eczema. The prevalence in the community is currently unknown but figures for children reviewed in secondary care settings range from 37% to 56%. The main foods triggering immediate reactions are cow's milk, egg and nuts. Immediate reactions to wheat, soya, fish and shellfish occur less frequently.

The child's age should be considered during history taking. Parents should be questioned about the pattern of atopic eczema in the child from birth. Allergy to cow's milk, egg and soya is less likely if atopic eczema developed after 2 years of age. History taking should include consideration of foods eaten, quantities (how much and how often), and foods not eaten in order to direct which foods to test for. The GDG believes that the following are signs of an immediate allergic reaction to food, although evidence was not specifically sought to assess this: widespread redness or rash, urticaria, increased itching, facial swelling, rhinitis, wheeze, cough, difficulty breathing, vomiting, abdominal pain, voice change, profound drowsiness, floppiness and/or loss of consciousness.

It is the GDG's view that children with atopic eczema who are suspected of having a food allergy should be referred for specialist investigation and management of the allergy. Owing to the heterogeneity of published diagnostic accuracy studies and the relative lack of data on costs for, or effectiveness of, tests for specific allergens in the age groups in which food testing is most likely to be required, the GDG felt unable to recommend any test for ruling out allergy. The 95% PPVs for some tests for different food allergens have been estimated in populations outside the UK and it is not certain whether these data are transferable to the UK population. Therefore, none of the tests can be used to rule in allergy and so the DBPCFC test remains the gold standard test for diagnosing food allergy.

For bottle-fed babies who are suspected of having a food allergy, the GDG consensus was that a trial of extensively hydrolysed formula milk should be offered. Although some European countries restrict this to casein-based formulas because they are thought to be less allergenic, there are only two such formulas on the market in the UK and the GDG did not consider there to be enough evidence of clinical or cost-effectiveness to justify this restriction in the NHS. Amino acid formulas are possibly better than casein-based formulas for promoting normal growth, but they are more expensive and they have not been demonstrated to be more cost-effective.

Goat's milk should not be offered to bottle-fed babies because it is nutritionally inadequate and shares 95% of cross-reacting allergens with cow's milk. Soya-based formulas contain phyto-oestrogens and are not recommended in the UK as the primary protein source in infants under 10 months. The GDG also considered that peanut allergy was more likely to develop if soya milk was consumed.

The GDG found little evidence to assess the effectiveness of elimination diets for breastfeeding mothers of children with atopic eczema. There was some support within the group for recommending elimination diets, but these were not already common practice in the NHS. The majority decision of the GDG was that women should be informed that the evidence base for elimination diets is thin but that they can be undertaken under the supervision of a specialist if food allergy is strongly suspected.

The GDG believes that there is not enough evidence to recommend house dust mite elimination measures or removal of pets, although it has been suggested that the timing of exposure to pets may affect the development of allergies. GDG discussion highlighted the possible negative psychological impact of removing pets from children. The house dust mite elimination strategies

evaluated in published clinical trials did not reflect current elimination practices. Elimination strategies may not be practicable in many cases.

Although the following potential trigger factors were explicitly mentioned in the guideline scope, the GDG did not find sufficient evidence to evaluate the effectiveness of their avoidance in the management of established atopic eczema: hard water, extremes of temperature or humidity, and stress. Nevertheless, the consensus view of the GDG based on their collective clinical experience was that humidity, stress or extremes of temperature could exacerbate atopic eczema in children and that they should be avoided where possible. The avoidance of irritants contained in topical preparations used to treat atopic eczema is considered in Chapter 7.

The GDG found no evidence which could be used to evaluate allergy testing in children with atopic eczema offered on the high street or over the internet (this could include conventional tests discussed above, and/or analysis of hair samples, Vega testing, etc). The GDG believes that any form of allergy testing outside a recognised clinical setting (such as the NHS) should be discouraged to avoid misinterpretation of results.

Recommendations for identification and management of trigger factors

When clinically assessing children with atopic eczema, healthcare professionals should seek to identify potential trigger factors including:

- irritants, for example soaps and detergents (including shampoos, bubble baths, shower gels and washing-up liquids)
- skin infections
- contact allergens
- food allergens
- inhalant allergens.

Healthcare professionals should consider a diagnosis of food allergy in children with atopic eczema who have reacted previously to a food with immediate symptoms, or in infants and young children with moderate or severe atopic eczema that has not been controlled by optimum management, particularly if associated with gut dysmotility (colic, vomiting, altered bowel habit) or failure to thrive.

Healthcare professionals should consider a diagnosis of inhalant allergy in children with seasonal flares of atopic eczema, children with atopic eczema associated with asthma or allergic rhinitis, and children aged 3 years or over with atopic eczema on the face, particularly around the eyes.

Healthcare professionals should consider a diagnosis of allergic contact dermatitis in children with an exacerbation of previously controlled atopic eczema or with reactions to topical treatments.

Healthcare professionals should reassure children with mild atopic eczema and their parents or carers that most children with mild atopic eczema do not need to have tests for allergies.

Healthcare professionals should advise children with atopic eczema and their parents or carers not to undergo high street or internet allergy tests because there is no evidence of their value in the management of atopic eczema.

Healthcare professionals should offer a 6–8 week trial of an extensively hydrolysed protein formula or amino acid formula in place of cow's milk formula for bottle-fed infants aged under 6 months with moderate or severe atopic eczema that has not been controlled by optimal treatment with emollients and mild topical corticosteroids.

Healthcare professionals should refer children with atopic eczema who follow a cow's milk-free diet for longer than 8 weeks for specialist dietary advice.

Diets based on unmodified proteins of other species' milk (for example, goat's milk, sheep's milk) or partially hydrolysed formulas should not be used in children with atopic eczema for the management of suspected cow's milk allergy. Diets including soya protein can be offered to children aged 6 months or over with specialist dietary advice.

Healthcare professionals should inform women who are breastfeeding children with atopic eczema that it is not known whether altering the mother's diet is effective in reducing the severity of the condition. A trial of an allergen-specific exclusion diet should be considered under dietary supervision if food allergy is strongly suspected.

Healthcare professionals should inform children with atopic eczema and their parents or carers that it is unclear what role factors such as stress, humidity or extremes of temperature have in causing flares of atopic eczema. These factors should be avoided where possible.

Research recommendations for identification and management of trigger factors

How effective and cost-effective is the use of house dust mite avoidance strategies in the treatment of childhood atopic eczema and which strategies, if any, are the most effective?

Why this is important
There are conflicting data on the effectiveness of using house dust mite avoidance strategies in the management of childhood atopic eczema. Many of the currently suggested techniques are time-consuming and expensive for parents/carers and it is important to establish their value.

When and how should children with atopic eczema be tested for allergies (skin prick tests, allergen-specific immunoglobulin E), and how can the diagnostic accuracy and effect on clinical outcomes of the tests be improved?

Why this is important
Parents and carers of children with atopic eczema often ask for allergy testing. However, there is confusion among clinicians about which tests are the most appropriate for different age groups. Interpretation of test results requires training and can be difficult because the diagnostic accuracy is uncertain; carrying out the tests is expensive and time-consuming and requires special training. The research should encompass clinical outcomes (for example, control of atopic eczema) in children who are diagnosed with allergies and undergo interventions to avoid exposure to relevant allergens. The results of the research will enable effective and cost-effective use of NHS resources.

How should exposure to pets be managed in children with atopic eczema; at what age does allergy occur and does tolerance develop?

Why this is important
Many children with atopic eczema show signs and symptoms of allergic reactions when in contact with animals such as cats, dogs and horses. However, clinical experience has found that many people report tolerance of their own pet but not others and this tolerance may be lost when teenagers move away from home. In cases of extreme allergy, some practitioners recommend the removal of the pet, while others suggest limited 'managed' exposure. There is a single abstract report of children choosing their pet as one of their three most favourite items and the psychological distress of pet removal may not be justified. Clear guidance is needed on the correct management of pet allergy in children with atopic eczema.

What is the optimal feeding regimen in the first year of life for children with established atopic eczema?

Why this is important
Dietary manipulation has the potential to decrease disease severity in children with proven food allergy. A study is needed to explore the potential benefits and harms of delaying the introduction of allergenic foods such as milk, egg and peanuts in infants with early signs of atopic eczema to assess the potential impact on atopic eczema severity and the subsequent development of food allergy, asthma and allergic rhinitis.

7 Treatment

Many of the treatments available for atopic eczema have been used in children. In this chapter, the evidence for each treatment is considered, starting with the most simple and moving on to more complex treatment options.

7.1 Emollients

The skin provides a barrier to the loss of water and penetration of irritants and allergens from the environment. The skin's outermost layer, the stratum corneum, provides the protective barrier, preventing water loss and controlling secretions via evaporation essential to keeping the skin's elasticity and firmness. In atopic eczema this barrier is damaged, both in eczematous areas and in clinically unaffected skin.

Atopic eczema has a strong genetic component. Filaggrin is a protein that is very important for the strength of the corneocytes (brick-like components) of the skin barrier. Changes in the filaggrin gene have been identified in children with atopic eczema. These changes result in an abnormal form of the filaggrin protein, which means that the corneocytes will not be as strong as in a child who does not have atopic eczema.[231] Interactions between genes responsible for the breakdown of the skin barrier and irritants such as soap and detergents can trigger flares of eczema.

Emollients (or moisturisers) act by occluding water loss from outer layers of the skin and by directly adding water to the dry outer layers of the skin, thereby providing a protective film over the skin to keep moisture in and irritants out. More than 30 different emollients and more than ten emollient bath additives are listed in the British National Formulary for Children (BNFC).[232] Emollients are available in a variety of formulations (ointments, creams, lotions, gels and aerosol sprays). Ointments, such as white soft paraffin and liquid paraffin, are greasy in nature whereas creams and lotions contain water and are more acceptable cosmetically. Creams, lotions and gels contain preservatives to protect against microbial growth in the presence of water. Antiseptics added to emollients include triclosan, chlorhexidine hydrochloride and benzalkonium chloride. See Table 7.1 for descriptions of the uses of the various types of emollient product.

Studies considered in this section

A health technology assessment (HTA) of treatments for atopic eczema was checked for RCTs evaluating the use of emollients in children.[26] Narrative reviews were also checked for studies of any design.[233,234] Where available, controlled trials evaluating the effectiveness of emollients in children with atopic eczema were considered for this section. Where RCTs were not available, studies of any design were considered.

Table 7.1 Types of emollient product

Type	Description
Emollient creams and ointments	These products are designed to be left on the skin. Creams soak into the skin faster than ointments.
Emollient soap substitutes	These products contain emollient ingredients with very mild emulsifiers. They are used instead of soap and other detergents.
Emollient semi-dispersing bath oils	These contain oils and emulsifiers that disperse the oil in the water. This combination has a cleansing effect if gently rubbed over the skin.
Non-dispersing emollient bath oils	These products contain oils with no emulsifying agent. The oil forms a layer on the surface of the water which is deposited on the skin as the child gets out of the bath.
Adjuvant emollient products	Some emollient products contain additional ingredients such as antipruritics and antiseptics.

Overview of available evidence

One RCT evaluated the use of emollients for the treatment of atopic eczema in children.[235] No clinical trials considered the quantity or frequency of use of emollients. No evidence was found for most of the emollients listed in the BNFC. Some evidence from studies of various designs were identified for aqueous cream,[236] emollients containing urea or ceramide,[68,237-239] an antimicrobial emollient,[240] and bath emollient preparations.[241-244] The steroid-sparing effect of emollients has also been considered in clinical studies.[245-248] Studies evaluating emollients in conjunction with topical corticosteroid wet wrap therapies are considered in Section 7.4.[249,250]

Moisturiser containing oat extract and evening primrose oil
One RCT in children (n = 76, age 6 months to 12 years) compared SCORAD and CDLQI after 8 weeks' twice-daily treatment with a moisturiser containing oat extract and evening primrose oil.[235] The control group received no emollient, but both groups used a standard cleansing bar and topical corticosteroids were permitted. There was a significant reduction in CDLQI in the treatment group (P = 0.001) but not in the control group (P = 0.17). There was no significant reduction in SCORAD in either group. No between-group analyses of these outcome measures were reported. [EL = 1−]

Aqueous cream
An audit of children attending a paediatric dermatology clinic recorded the proportion of immediate cutaneous reactions to emollients (defined as one or more of burning, stinging, itching and redness developing within 20 minutes of application). Aqueous cream was the emollient used by most (71%), which was associated with an immediate cutaneous reaction in 56% of exposures, compared with 18% with other emollients used (details of the other emollients were not reported; n = 100).[236] [EL = 3]

Preparations containing urea
Three studies evaluated preparations containing urea. None of the studies provide usable data for children with atopic eczema. One that compared urea 10% with betamethasone valerate 0.1% (a topical corticosteroid) in a within-patient (left–right side) trial in children with atopic eczema only reported the extent of improvement after 10 days' treatment, providing no demographic data for the children nor numerical data for outcomes.[237] Two other studies evaluating preparations containing urea were identified: in one of these it was not possible to tell whether any of the individuals treated were children with atopic eczema,[238] and in the other no data were reported for the minority of children with atopic eczema.[239]

Ceramide-containing emollients
A within-patient (left–right side) comparison reported the use of a ceramide-containing emollient in addition to usual treatment for up to 20 weeks in children with atopic eczema (n = 24). The outcomes considered were severity (SCORAD) and skin parameters (transepidermal water loss, hydration, and integrity of the stratum corneum). However, results were only presented in graphs in the trial report, with no numerical data.[68] [EL = 2−]

Bath emollients
Four studies considered the use of bath oil preparations; three provided some effectiveness data.[241-244] Two studies which evaluated preparations containing antimicrobials[241,243] are considered in Section 7.6.

A case series reported the use of a bath oil preparation containing soya oil plus lauromacrogols in children and young people with dry, itchy dermatoses (n = 3566). The diagnosis was atopic eczema in 86% of the cases, and most (94%) of those included were aged under 15 years. The bath oil was used daily by 13%, three times a week by 38%, twice a week by 42%, and once a week by 7%. Mean duration of treatment and follow-up was 6 weeks. Overall, 78% received other treatment for their skin condition, although details of these treatments were not reported. Therefore it is not known whether the improvements in the children's global condition were due to the emollient or to other treatments. The study provided information on tolerability, with skin reactions reported in 0.28%. The reactions were described as mostly mild, and included burning, itching and reddening. Physician's assessment of tolerability was 'good' in 97% of children.[242] [EL = 3]

Frequency of bathing

The effects of using a bath emollient daily (by soaking one arm in a basin of water with added emollient) was evaluated in a within-patient (left–right side) comparison (n = 9). All children had standardised treatment consisting of weekly whole-body bathing in a bath containing the same emollient (Oilatum®), twice-daily application of an emollient and a topical corticosteroid, and use of emulsifying wax as soap substitute. The treated (daily treatment) and untreated (routine care) arms were evaluated by an assessor blind to treatment allocation. The mean difference in clinical score at 4 weeks (a measure of extent and severity of atopic eczema) was not significant, although the difference in the mean change in score over the duration of the 4 week study was reported to be significantly different.[244] [EL = 2−]

Studies evaluating the steroid-sparing effect of emollients

Three controlled trials sought to evaluate the steroid-sparing effects of emollients.[245,246,248] They all compared the use of an emollient plus a topical corticosteroid with a topical corticosteroid used alone.[245,246] A lack of baseline data meant it was not known whether the groups were similar other than in the interventions made. [EL = 2−] Additionally, it was not clear in either study whether daily quantities of topical corticosteroids applied in the once-daily versus twice-daily groups were similar.

The first study was an RCT in infants (n = 162) comparing micronised desonide 0.1% (high potency) and/or desonide 0.1% (moderate potency) to the respective treatments plus an emollient containing evening primrose oil and oat extract.[248] Emollient was applied twice daily to dry, non-inflamed areas of skin over the whole body in the treatment group and tubes of topical corticosteroid were weighed at 0, 3 and 6 weeks to assess the amount used by all participants. At 6 weeks, there was a significant difference between the treatment groups in the amount of high potency corticosteroid used (mean difference 6.14 g, P = 0.025). There were no significant differences in the amount of moderate potency topical corticosteroid used, SCORAD severity index or quality of life. Two participants experienced severe adverse effects and discontinued treatment. [EL = 1−]

The second study compared the effectiveness of hydrocortisone cream 2.5% applied twice daily with a regimen of hydrocortisone cream 2.5% plus an emollient, both applied once daily (n = 25). After 3 weeks' treatment improvements in signs and symptoms of atopic eczema were reported in both groups, with no statistically significant difference between groups. However, there was poor reporting of outcomes.[245] [EL = 2−]

The third study (n = 50) compared betamethasone valerate 0.1% applied twice daily with betamethasone valerate 0.1% applied in the morning and an emollient applied in the evening. After 4 weeks' treatment there were no significant differences in improvements in SCORAD scores (P values were not stated). No adverse effects were reported during the trial.[246] [EL = 2−]

A 1989 German trial compared the effects of fluprednidene 21 acetate (a topical corticosteroid; potency not reported) used twice daily without an emollient for 3 weeks with three other treatment regimens that involved using fluprednidene 21 acetate and its emollient base (n = 44). The three other groups were treated with the following:

- fluprednidene 21 acetate on days 1 and 3 and emollient on day 2 (repeated until day 21)
- fluprednidene 21 acetate on days 1 and 4, and emollient on days 2 and 3 (repeated until day 21)
- fluprednidene 21 acetate on days 1 and 5 and emollient on days 2–4 (repeated until day 21).

The trial was published in German, but was summarised in an English language review paper.[247] [EL = 3] It was not clear whether the patients were children or adults (or a mixture of the two). The study found that clinical outcomes (severity) were similar in the fluprednidene 21 acetate only group to the other three groups. The group using emollients for most days used 75% less fluprednidene 21 acetate than the group using the fluprednidene 21 acetate only. No numerical data were reported in the English language review paper.[247]

Cost-effectiveness

No cost-effectiveness studies were identified that addressed this clinical question.

Evidence statement for emollients

There was a lack of studies of any design that evaluated the effectiveness of emollients in children with atopic eczema. The available data consisted of isolated case series and case reports, with no controlled studies comparing emollients to placebo/no active intervention. With no control groups, it was not possible to quantify the benefits or harms of emollient therapy. Irritant adverse skin reactions such as stinging were documented to occur with emollients such as aqueous cream and bath oils. [EL = 3]

Case series that considered the effects of treatment with emollients containing antimicrobial agents (including bath oils) in children reported subjective global measures of improvement over the short term only (2–6 weeks). In these case series, children received other treatments and thus it was not possible to identify which treatment produced benefit. [EL = 3]

Although emollients are widely described as having a steroid-sparing effect, no robust data were identified to confirm or refute this. [EL = 2−]

From evidence to recommendations

The GDG believes that emollients are the most important treatment for atopic eczema because they restore the defective skin barrier. A complete emollient regimen produces optimum benefit. This involves avoidance of products that may irritate the skin or lead to breakdown of the skin barrier, including soaps, shampoo products and perfumed products obtained over the counter or on prescription. Adherence to an emollient regimen has the potential to reduce the need for more expensive treatments and associated GP consultations.

All children require an essential package of emollient therapy including a topical emollient and a wash product. A single emollient may satisfy both these functions. However, some children will require more than one product to ensure adequate emollient coverage. One of the most important environmental factors in triggering atopic eczema is soap and detergents. There are high levels of *Staphylococcus aureus* on the skin of children with atopic eczema (see Section 6.1) which are also an important trigger for flares of atopic eczema. Emollient bath oils and other emollient wash products provide an essential method to clean the skin without the damaging effect of soap and detergents.

Healthcare professionals should offer a range of different products to children with atopic eczema for topical application and for washing, and children should be encouraged to try out various combinations of topical products. The correct emollient is the one that the child will use.

Not all types of emollients suit all people. Adherence to emollient treatment is the key to successful therapy for atopic eczema. Children may have adverse reactions to some products, or may not like the way they feel on their skin. Topically applied emollients may be easier to apply on some children who can tolerate standing still for a period of time several times a day. Other children may need additional products that can be applied indirectly to the skin, such as in the bath, to ensure that adequate amounts of emollient are absorbed into their skin. Children's preferences and tolerance for specific products will differ over time as they get older and their lifestyle and attitudes change. In addition, some bath products contain added ingredients (such as antimicrobials) that may be useful for short periods of time to manage specific conditions.

It is the GDG's view that the practice of repeat prescribing of the same emollient products over long periods of time without review should be discouraged.

Idiosyncratic skin reactions/irritations and lifestyle may influence the choice of emollient. Since there is little cost difference between proprietary products, these factors should be taken into account when selecting an emollient in order to improve adherence to therapy. Although non-proprietary products are cheaper, they are often less acceptable to children and are not, therefore, usually suitable as a first-line treatment. Aqueous cream is associated with stinging when used as a leave-on emollient but can be used as a wash product. Since an emollient's effectiveness and acceptability can change over time for a particular child, children and their parents/caregivers need to be encouraged to look for the signs that an emollient is no longer providing maximum benefit (for example, the return of symptoms of atopic eczema) and to seek the advice of a

healthcare professional if they have concerns. They should then be offered an opportunity to try a different product or combination of products. [EL = 4]

Skin reactions, including stinging, are a manifestation of worsening eczema (breakdown of the skin barrier). Emollients are the mainstay of current treatment of atopic eczema, and clinical experience is that they reduce the need for topical corticosteroids. Regular use of emollients is essential to ensure rehydration of the skin, and to give skin flexibility. It is the experience of the GDG that dry skin requires a greasy emollient preparation, whereas red inflamed eczema usually responds better to water-based products because evaporation cools the skin. Other treatment for red inflamed eczema is discussed in Sections 7.2 and 7.7. [EL = 4]

The GDG's view is that the effects of emollients are short-lived. Therefore, they should be used frequently and in large quantities, particularly after bathing or washing, in order to protect the integrity of the skin barrier. The frequency of use of the emollient will depend on the dryness of the child's skin and the type of emollient used. It is the experience of the GDG that children with generalised atopic eczema typically require about 250 g per week or more of an emollient. This should far exceed the quantities of other treatments. [EL = 4]

It is the GDG's view that the need for frequent application of emollients implies that children should have access to emollient therapy at nursery, pre-school or school. [EL = 4] The GDG noted that the selection of emollient preparations prescribed for each child could include conveniently sized containers for use outside the home (as well as large containers for use at home).

The GDG believes it is good practice to apply emollients by smoothing them into the skin in the direction of hair growth, rather than rubbing them in, to facilitate absorption and reduce the possibility of occlusion folliculitis. Rubbing introduces air which makes absorption more difficult. [EL = 4]

Recommendations for emollients (including research recommendations) are presented in Section 7.11.

7.2 Topical corticosteroids

Topical corticosteroids are derived from the naturally occurring corticosteroid cortisol (hydrocortisone) which is secreted by the adrenal cortex. Corticosteroids have anti-inflammatory and immunosuppressant effects, as well as other actions relevant to their effects on skin including inhibiting fibroblast proliferation and collagen synthesis, and local vasoconstriction.

Twenty topical corticosteroids are listed in the BNFC. They are available in a variety of formulations, including ointments, creams, and lotions. The available products also differ in potency (see Table 7.2). In the UK topical corticosteroids are divided into four categories: mild, moderate, potent and very potent. The potency of topical corticosteroids is usually determined by a vasoconstrictor assay that measures the degree and duration of blanching of the skin produced by topical application.[251,252]

The potency of a topical corticosteroid is not necessarily related to its concentration – it also depends on the specific modification (esterification) of the steroid molecule. For example, hydrocortisone (acetate) 1% is a mild preparation, but hydrocortisone butyrate 0.1% is a potent preparation. The clinical effect of a topical corticosteroid preparation depends on its potency, concentration and the formulation (vehicle/base).

The finger-tip unit[253] is a validated method for applying topical corticosteroids in safe quantities. One finger-tip unit is a squeeze of cream or ointment along the index finger from the tip to the first finger joint. This weighs approximately half a gram and will cover a surface area of two adult hands (including the fingers). This information is often included in patient information leaflets.

Overview of available evidence

The HTA of treatments for atopic eczema was checked for evidence relating to children.[26] Where available, RCTs evaluating the effectiveness of topical corticosteroids in children with atopic eczema were considered for this section. Where RCTs were not available, or were too short in duration to consider adverse effects, observational studies of any design were considered.

Table 7.2 Potency of topical corticosteroids[a]

Topical corticosteroid	Potency
Desonide 0.05%[b]	Mild
Hydrocortisone (acetate) 0.1–2.5%	Mild
Alclometasone dipropionate 0.05%	Moderately potent
Betamethasone valerate 0.025%	Moderately potent
Clobetasone butyrate 0.05%	Moderately potent
Fludroxycortide 0.0125% (formerly known as flurandrenolone)	Moderately potent
Fluocinolone acetonide 0.00625%	Moderately potent
Flucortine butylester 0.75%[b]	Moderately potent
Fluocortolone	Moderately potent
Hydrocortisone valerate 0.2%[b]	Moderately potent
Prednicarbate 0.25%[b]	Moderately potent
Beclometasone dipropionate 0.025%[b]	Potent
Betamethasone dipropionate 0.05%	Potent
Betamethasone valerate 0.1%	Potent
Diflucortolone valerate 0.1%	Potent
Fluocinolone acetonide 0.025%	Potent
Fluocinonide 0.05%	Potent
Fluticasone propionate 0.05%	Potent
Hydrocortisone butyrate 0.1%	Potent
Mometasone furoate 0.1%	Potent
Triamcinolone acetonide 0.1%	Potent
Clobetasol propionate 0.05%	Very potent
Diflucortolone valerate 0.3%	Very potent
Halcinonide 0.1%[b]	Very potent

[a] Potency taken from the BNFC 2007.[232]

[b] Products containing these topical corticosteroids are not available in the UK.

The NICE TA programme issued guidance on the frequency of application of topical corticosteroids in 2004.[12] That guidance, which is adopted in this guideline, applies to both children and adults with atopic eczema. The HTA informing the NICE guidance included three studies involving children.[12] No further RCTs considering frequency of application were identified.

Overall, ten RCTs compared topical corticosteroids of different potencies,[254-263] four RCTs compared topical corticosteroids with other interventions (coal tar[264] and topical calcineurin inhibitors[265-267]) and two RCTs compared different formulations of the same topical corticosteroid.[268,269] Limited data comparing topical corticosteroids with placebo or no intervention in children only were found,[270] and therefore studies that included both children and adults were also considered.[271-273] Studies considering the steroid-sparing effects of emollients[245,246,248] were described in Section 7.1.

Eight other reviews or studies of other design that considered only safety were also identified.[274-281] One review of the safety of topical therapies for atopic eczema was identified, but no conclusions could be drawn in relation to children.[282]

No studies evaluating the use of the following topical corticosteroids in children with atopic eczema were identified: betamethasone valerate 0.025%, fludroxycortide (formerly known as flurandrenolone), fluocinolone acetonide 0.00625% or 0.025%, fluocortolone, beclometasone, betamethasone dipropionate 0.05%, diflucortolone 0.1% or 0.3%, fluocinonide 0.05% or clobetasol propionate 0.05%.

RCTs comparing topical corticosteroids with vehicle

One short-term (7 day) double-blind RCT reported the change in clinical score in children aged 4.5 months to 15 years with atopic eczema who were treated with desonide (a mild preparation) compared with its vehicle base (n = 40). The proportion showing improvement or clearance of their condition was significantly higher in the desonide group (67%) than in the vehicle group (16%, $P < 0.001$).[270] [EL = 1+]

Other RCTs comparing a topical corticosteroid with placebo/vehicle included both children and adults, although none reported the proportion of children aged under 12 years and nor did they report data separately for this group.[271-273] Each was a within-patient (left–right side) randomised double-blind comparison.

The first study compared hydrocortisone valerate 0.2% cream (moderately potent) with 'placebo' cream (no further details provided; n = 20).[271] The creams were applied three times a day for 2 weeks. Although the study reported the proportion with clearance of the condition, no other details or numerical data were given. Clearance was reported for eight patients treated with hydrocortisone valerate 0.2% and in one treated with placebo.[271] [EL = 1−]

The second study compared halcinonide 0.1% ointment (very potent), applied three times a day, with its vehicle base (n = 233, 92% completed and analysed). The global response was reported, though it was not clear exactly what was measured or how. The proportions with an excellent or good response were 85% and 44% in the halcinonide and placebo groups, respectively ($P < 0.001$).[273] [EL = 1−]

The third study, in patients with mild to moderate atopic eczema, compared desonide 0.05% (mild potency) plus an emollient with desonide 0.05% alone (n = 80).[272] After 3 weeks' treatment, the reduction in severity score was significantly greater in the group treated with desonide plus emollient compared with desonide alone (80% versus 70%, respectively, $P < 0.01$). Global improvement of 75% or more was reported by 70% versus 55%, respectively ($P < 0.01$). Quantities of topical corticosteroid used were not reported. The proportions reporting burning or stinging on application during the first week of treatment were similar (12% versus 14%).[272] [EL = 1+]

RCTs comparing different topical corticosteroids

Ten RCTs compared the effectiveness of topical corticosteroids of different potencies in children of various ages (2 months to 15 years), the majority including only children aged under 12 years with atopic eczema of varying severity.[254-263] Five of these studies did not state whether an emollient was also used;[254,258,259,262,263] two studies did not permit the use of emollients;[256,260] in the remaining three studies emollients could be used as required.[255,257,261] The comparisons were:

- two moderately potent preparations (one RCT)[263]
- potent versus mild preparations (five RCTs)[254-256,258,283]
- potent versus moderately potent preparations (four RCTs)[257,259,261,262]
- two potent preparations (one RCT).[255]

No trials compared moderately potent with mild potency topical corticosteroids. Few studies reported the quantities of topical corticosteroids used – where this information was given, the findings are summarised in this section.

Alclometasone dipropionate 0.05% (moderately potent) versus clobetasone butyrate 0.05% (moderately potent)

One double-blind RCT compared the effectiveness of alclometasone dipropionate 0.05% with clobetasone butyrate 0.05% (n = 43). In this small study, improvement in severity of signs and symptoms was not significantly different between groups. Investigator's rating of the global condition was similar in both groups. Stinging was reported in two children treated with alclometasone.[263] [EL = 1+]

Triamcinolone acetonide cream 0.1% (potent) versus hydrocortisone valerate cream 0.2% (moderately potent)

A within-patient (left–right) RCT compared 2 weeks' triamcinolone acetonide 0.1% treatment with hydrocortisone 0.2% (n = 66, 54 completed and analysed). Severity was reported to be improved

in both groups, but data were only shown in graphs. Clearance or an 'excellent response' was seen in 74% in both groups. Transient stinging was reported in 3% in both groups.[283] [EL = 1−]

Hydrocortisone butyrate 0.1% cream (potent) versus hydrocortisone 1% ointment (mild)
One RCT evaluated two hydrocortisone preparations in a left–right comparison (hydrocortisone butyrate 0.1% cream versus hydrocortisone 1% ointment, *n* = 40). Treatment was given for 4 weeks. Significantly greater improvements in the global severity of the condition were reported in children treated with hydrocortisone butyrate 0.1%: mean (%) reduction in global severity score after 4 weeks of 2 (73%) versus 1.6 (62%), $P < 0.05$. Details of any adverse effects were not reported.[258] [EL = 1+]

Betamethasone valerate 0.1% (potent) versus hydrocortisone 1% (mild)
One double-blind RCT compared the effectiveness of 3 days' treatment with betamethasone valerate 0.1% with 7 days' treatment with hydrocortisone 1% ointment in children with mild to moderate atopic eczema (*n* = 207).[254] Treatment was used when needed during an 18 week period. The population consisted predominantly of children from the community in whom atopic eczema was milder than in the 16% recruited from a hospital outpatient clinic. Several outcomes were only reported for the community subgroup. After 18 weeks' follow-up, no significant differences were found between groups in any outcome (scratch-free days mean difference 0.5 days, 95% CI −0.2 to 4.0 days, changes in quality of life scores (CLQI and DFI) or in the number of relapses or disturbed nights). Overall, 9% reported adverse events, which were mainly worsening of symptoms in 5% and 9% of the groups treated with the potent and mild topical corticosteroids, respectively. Other adverse events reported were cases of spots, rashes, hair growth and viral encephalitis in the group treated with betamethasone valerate 0.1%. Fifty percent of children who responded to a follow-up questionnaire expressed a preference for using a mild topical corticosteroid if it controlled the atopic eczema successfully. The remaining 50% of children who responded to the questionnaire expressed a preference for using a short burst of betamethasone because it reduced treatment time and controlled the atopic eczema quickly.[254] [EL = 1+]

Mometasone furoate 0.1% (potent) versus various hydrocortisone preparations
Two RCTs compared mometasone furoate 0.1% with various hydrocortisone preparations in children with moderate to severe atopic eczema.

In the first study the comparator was hydrocortisone valerate 0.2% cream (moderate potency *n* = 219).[256] The children had failed to respond to treatment with a hydrocortisone preparation (assumed to be a mild preparation) over the previous 7 days. It was reported that there were no significant differences between mometasone furoate 0.1% and hydrocortisone valerate 0.2% groups in global improvement (87% versus 78%, $P = 0.01$) after 3 weeks' treatment. However, no baseline data were reported and thus it was not possible to determine whether groups were similar other than in the intervention being given.[256] [EL = 1−]

In the second RCT the comparator was hydrocortisone 1% cream (*n* = 48). After 6 weeks' treatment, significantly greater improvement in disease severity was reported in the mometasone group (95% versus 75% with hydrocortisone 1%, $P = 0.01$), and greater reduction in the total body surface area involved (reductions of 40% and 26%, respectively, $P = 0.03$). Overall, 63% in both groups discontinued treatment early owing to clearance of their condition. There was no significant difference between the two groups in mean morning plasma cortisol levels or in any changes in these levels, although numerical data were not reported.[260] [EL = 1+]

Fluticasone propionate 0.05% (potent) versus hydrocortisone 1% (mild) or hydrocortisone 17-butyrate 0.1% (potent)
One publication reported the outcomes of two RCTs which compared fluticasone propionate 0.05% cream with hydrocortisone 1% (*n* = 137) or hydrocortisone 17-butyrate 0.1% (*n* = 128) in children experiencing a flare of atopic eczema.[255] Treatment was applied twice a day for 2–4 weeks until the atopic eczema was stabilised, followed by intermittent use as required up to twice a day, for up to 12 weeks. Emollients could be used as required.

Greater improvement in total eczema score (a measure of three signs and the surface area affected) was reported with fluticasone compared with the hydrocortisone preparations in both studies at the end of both the acute and maintenance treatment phases. Also, significantly

greater improvements in rash, itch and sleep disturbance were reported with fluticasone versus hydrocortisone 1%, and itch and sleep disturbance only with fluticasone versus hydrocortisone 17-butyrate 0.1%. Physicians considered that 84–98% of children had improved from baseline, the difference between groups being statistically significant for the fluticasone versus hydrocortisone 17-butyrate study. Time to recurrence was also reported, but no statistical analysis was presented. The quantities of topical corticosteroids used were similar in both studies. Adverse effects considered to be related to treatment were cases of folliculitis and tinea (ringworm), and development of red papules/boils with fluticasone; a case of flare with secondary infection with hydrocortisone 1%; and cases of itchy skin, minor skin infections/pustules, and impetigo on the face with hydrocortisone 17-butyrate 0.1%.[255] [EL = 1+]

Triamcinolone acetonide 0.1% cream (potent) versus alclometasone dipropionate cream 0.05% (moderately potent)

One RCT compared triamcinolone acetonide 0.1% cream with alclometasone dipropionate 0.05% cream (n = 40). Treatment was used for up to 3 weeks. Improvements in severity of four signs and symptoms (erythema, lichenification, pruritus and exudation) were reported to be significantly greater with triamcinolone. Early-morning serum cortisol levels were measured in 68% of the children: no significant changes were reported, but mean differences from baseline were not quoted for the two treatment groups.[257] [EL = 1+]

Mometasone furoate 0.1% (potent) versus clobetasone (ester not specified) 0.05% (moderately potent)

One RCT compared the effectiveness of mometasone furoate 0.1% and clobetasone 0.05% (n = 60). Mometasone was applied once daily and clobetasone twice daily. After 3 weeks' treatment, there was significantly greater reduction in disease severity score with mometasone (86% versus 66% improvements, $P < 0.01$). The proportions of children with total clearance or improvement of the target area were: clearance 50% versus 7%, marked improvement 30% versus 37%, and moderate improvement 20% versus 50%. No adverse effects were reported during the trial.[259] [EL = 1+]

Fluticasone propionate cream 0.05% (potent) versus clobetasone butyrate cream 0.05% (moderately potent)

One double-blind RCT compared fluticasone propionate 0.05% cream applied once daily with clobetasone butyrate 0.05% cream applied twice daily (n = 22).[261] Treatment was given for up to 4 weeks, with an additional 2 weeks' follow-up. There were no significant differences between groups in any outcomes (changes in SCORAD severity scores and 24 hour urinary cortisol excretion). In one child treated with clobetasone butyrate 0.05% cream, urinary cortisol excretion decreased during the study, but it had recovered by the follow-up visit.[261] [EL = 1+]

Hydrocortisone butyrate 0.1% (potent) versus alclometasone dipropionate 0.05% (moderately potent)

One double-blind RCT compared the effectiveness of alclometasone dipropionate 0.05% to hydrocortisone 17-butyrate 0.1% (n = 40). Improvement in severity of signs and symptoms was not significantly different between groups after 2 weeks' treatment. Investigator's rating of the global condition was similar in both groups. Stinging was reported in two children treated with alclometasone and in one treated with hydrocortisone.[262] [EL = 1+]

Comparisons with desonide (mild)

Two RCTs compared hydrocortisone 2.5% ointment or mometasone furoate 0.1% with desonide (a mild topical corticosteroid not available in the UK).[284,285] These studies are considered in this section because they provided some safety data for hydrocortisone and mometasone.

After a mean of 27 days' (maximum 42 days') treatment with mometasone, 'evidence of atrophy' was reported in four children (17%); this was assessed by measuring the following signs on a four-point scale: thinning of the skin, striae, shiny skin, telangiectasia, loss of elasticity, and loss of normal lines on the cutaneous surface. Other adverse effects reported were burning on application in three children and appearance of fine hair in one child (n = 13).[284] [EL = 3]

After 4 weeks' treatment with hydrocortisone 2.5% ointment there were no significant differences in early-morning serum cortisol levels in response to an adrenocorticotrophic hormone (ACTH) test compared with baseline (mean change 1.3%) (*n* = 10).[285] [EL = 3]

Different formulations of a topical corticosteroid of the same potency

Two within-person (left–right side) RCTs evaluated the global effectiveness and cosmetic acceptability of two different formulations of hydrocortisone 1% (an oil-in-water emulsion, and an ointment) in children with atopic eczema (total *n* = 156).[268,269] Treatment was given for 4 weeks. Neither study reported baseline or demographic data, other than severity scores, and one did not report statistical analysis.[269] The other found no significant difference between the two preparations in global improvement, but there was a significant difference in patient preference, with more preferring the emulsion than ointment.[268,269] [EL = 1−]

Different frequency of application

The NICE TA programme issued guidance on the frequency of application of topical corticosteroids in 2004.[12] The guidance applies to both children and adults with atopic eczema. The HTA informing the NICE guidance[12] included three studies involving children, only two of which have been published in full.[286,287] Data for the third study are reported in the HTA.[288] No further RCTs considering frequency of application were identified.

The available studies compared once-daily with twice-daily application of clobetasone 17-butyrate 0.05% lotion (*n* = 30),[287] fluticasone propionate 0.05% cream (*n* = 126)[286] and fluticasone propionate 0.005% ointment (*n* = 120).[288] The two trials involving fluticasone included both children and adults but data for children were reported separately. No significant differences were reported in outcomes following once- or twice-daily application of clobetasone 17-butyrate 0.05% lotion for 1 week, or fluticasone propionate 0.05% cream for 4 weeks. The RCT evaluating fluticasone propionate 0.005% ointment, which was reported only within the HTA, found that both investigator- and patient-rated success rates after 4 weeks' treatment were significantly higher in the group using twice-daily application of the ointment.[288] [EL = 1++]

Other studies of topical corticosteroids that focused on adverse effects

A post-marketing safety review of topical corticosteroids in paediatric patients (mean age 7.7 years) documented the adverse effects reported between 1987 and 1997 (*n* = 202).[281] The body areas to which the topical corticosteroid was applied were the face and neck (20%), buttock, groin or genitals (16%), legs or feet (11%), arms or hands (10%), head or scalp (6%), trunk (4%), whole body (2%), or axillae (1%). The adverse effects occurring in 1% or more children were local irritation (33%), skin depigmentation or discolouration (15%), striae or skin atrophy (15%), Cushing syndrome (3%), growth retardation, hyperglycaemia, scarring and staphylococcal infection (each 2.5%), genital hypertrichosis, hirsutism and rosacea (each 2%), acne, glaucoma and hypersensitivity reaction (each 1.5%), and adrenal insufficiency, bruising, fungal infection, gynaecomastia, perioral dermatitis and mood change/'mental status' (each 1%).[281] [EL = 3]

Several case series or before-and-after studies considered the impact of topical corticosteroid treatment on adrenal function by measuring serum cortisol and/or ACTH levels.[274–279,289] [EL = 3]

Two studies reported no significant changes in cortisol or ACTH levels or response to a short tetracosactride test after 1–4 weeks' use of clobetasone butyrate 0.05% (total *n* = 41).[274,275] [EL = 3]

No significant differences were found between pre- and post-treatment serum cortisol values (adrenal response to stimulation with tetracosactride) in children treated with fluticasone propionate 0.05% cream twice daily for up to 4 weeks (*n* = 51).[276] Two children did not attain the usual response (minimum cortisol level) expected, and were considered to have adrenal suppression. Drug-related adverse effects reported were burning, urticaria, erythematous rash and telangiectasia.[276] [EL = 3]

A safety study of fluticasone propionate 0.05% lotion (*n* = 44, age 3 months to 6 years) found no difference in cortisol levels after up to 4 weeks' treatment compared with baseline in children with moderate to severe atopic eczema.[290] [EL = 3]

One study compared serum cortisol levels in children treated with one of six different topical corticosteroids of different potencies (some not available in the UK): betamethasone dipropionate, diflucortolone valerate, halcinonide, clobetasone butyrate, desonide and flucortine butylester (n = 26).[277] After 6 days' treatment, plasma cortisol values decreased most from baseline with diflucortolone valerate (72%), followed by betamethasone dipropionate (61%), halcinonide (38%) and clobetasone butyrate (21%). Mean plasma cortisol values increased slightly with desonide and with flucortine butylester (1% and 15%, respectively). For those treated with diflucortolone, betamethasone and halcinonide, the cortisol levels fell below the normal range in 4/4, 4/5, and 2/4 children, respectively, during the first 6 days of treatment, and these levels normalised in 3/4, 2/4 and 2/2 children during continued treatment (no further details were provided). Of those treated with clobetasone, desonide or flucortine, none of the serum cortisol values fell outside the normal limits. These data should not be regarded as comparisons of the effects of the six products on cortisol levels, because as well as differences in potencies, the age of the children and the body surface area treated would influence systemic absorption of the topical corticosteroid, and these confounders were not accounted for in this study.[277] [EL = 3]

Two cross-sectional studies compared adrenal response to a low-dose ACTH stimulation test in children with atopic eczema with the response in a control group. The children in both studies had been treated with topical corticosteroids since infancy. The first study included only children who had been treated with hydrocortisone 1% ointment (median duration 6.5 years, range 3–10 years; n = 28). None of the plasma cortisol measurements differed significantly between the two groups (basal, peak, increment or area-under-curve measurements).[278] [EL = 3] The second study included children treated with topical corticosteroids of different potencies (median duration 6.9 years, range 0.5–17.7 years; n = 35).[279] This study also reported no significant differences in adrenal response to ACTH between children treated with mild or moderately potent topical corticosteroids and controls. All four children treated with potent or very potent topical corticosteroids failed the ACTH test (failure was not defined; it was assumed that the 'normal' response was not attained).[279]

A retrospective study (n = 1271, 666 children) evaluated adverse effects to topical corticosteroids of various potencies, although it was not clear which products fell into which classification of potency used in the study.[280] Treatment was used for at least 6 months. The cumulative incidence of several adverse effects increased with age (infants versus children): hypertrichosis (0.5% versus 1%), telangiectasia on cheeks (0% versus 2.3%), skin atrophy of antecubital or popliteal fossae (1.5% versus 5.2% and 1.9% versus 4.1%, respectively), acne and folliculitis (0% versus 1.3%), bacterial infection (1.4% versus 2.1%), and steroid-induced and contact dermatitis (0% versus 0.4% for both outcomes). There were no reports of striae atrophica. Cumulative incidence of fungal infection fell (1.9% versus 0.6%). The risk of telangiectasia on the cheeks appeared to be higher in those with longer duration of disease, and in those who applied more than 20 g to the face during the 6 month treatment period. The risk of atrophy of the antecubital and popliteal fossae was higher with longer duration of disease, and in those who used more than 500 g of topical corticosteroid during the treatment period.[280] [EL = 3]

Topical corticosteroid versus a coal tar preparation

One within-patient (left–right side) RCT compared the effectiveness of a coal tar 1% cream to hydrocortisone 1% cream in children with dry, bilateral, symmetrical atopic eczema (n = 30).[264] Treatment was used for 4 weeks. Use of emollients was not permitted. Confidence intervals for mean differences between groups in improvement in severity scores were not reported, but it was stated that there were no significant differences. This small study may have been underpowered to detect differences. No baseline data were reported (other than for severity scores), so it could not be determined whether groups were similar at baseline.[264] [EL = 1−]

Topical corticosteroids versus topical calcineurin inhibitors

Evidence for this comparison is considered in Section 7.3.

Studies that have investigated the effectiveness of topical corticosteroids for preventing recurrence of flares are considered in Section 7.7.2. Studies that have investigated the effectiveness of topical corticosteroids in combination with antibiotics for treating infected atopic eczema are considered in Section 7.6.

Cost-effectiveness

No published economic evaluations of topical corticosteroids were identified. The NICE TA included an economic analysis on frequency of use of topical corticosteroids but the analysis did not distinguish between children and adults.[288] The clinical outcomes were reported in the TA to be equivalent and thus the cost-effectiveness analysis was an analysis of costs of treatment only.

The TA stated that where there is no clear difference in clinical outcome by frequency, the choice of treatment should be guided by cost per patient treated, taking into account product costs at that point in time and frequency of use. The TA concluded that, given the small cost difference between regimens, any treatment would be highly likely to be cost-effective if it could demonstrate better outcomes than other topical corticosteroid treatments. Also, better outcomes would be likely to reduce the need for additional GP visits to address problems associated with treatment failure.

The cost savings associated with once-daily treatment were calculated using various scenarios (number of flares per year and quantities of topical corticosteroid used and wasted). However, given the lack of clinical evidence for this, or any other basis on which to make a reasonable judgement on the percentage of products used and wasted in any treatment period, the TA was not able to conclude with any certainty whether once-daily use of topical corticosteroids would lead to cost savings for the NHS.

Since no economic evaluation studies were identified that considered the cost-effectiveness of topical corticosteroids of different potencies, it was not possible to assess whether the additional number of successful treatments using topical corticosteroids of higher potency were 'worth' the additional costs associated with treatment, taking into account the small risk of harmful side effects associated with more potent topical corticosteroids.

Evidence statement for topical corticosteroids

Few trials have evaluated topical corticosteroids in a way that reflects their use in UK practice (that is, management of flares/exacerbations in children already using emollients). RCTs that compared 2–4 weeks' treatment with a topical corticosteroid with vehicle in children and adults generally reported a greater response rate in the topical corticosteroid group, although a noticeable effect of vehicle (emollient) was apparent. [EL = 1−] Greater efficacy was seen in an RCT comparing an emollient used with a mild topical corticosteroid with the topical corticosteroid used alone (one trial). [EL = 1+]

In comparisons of two formulations of mild topical corticosteroids, there were differences in patient preference but no differences in clinical outcomes. [EL = 1−] No significant differences were identified between two moderately potent preparations (one trial). [EL = 1+]

Compared with mild preparations, potent topical corticosteroids generally led to significantly greater improvements in outcomes (severity and global improvements) following 2–6 weeks' treatment, although only one of the available studies evaluated quality of life. [EL = 1+] The outcome of 3 days' treatment with betamethasone valerate 0.1% (potent) was not significantly different to 7 days' treatment with hydrocortisone 1% (mild) in one trial involving children with mild to moderate atopic eczema treated mainly in the community. [EL = 1+] No consistent differences in effectiveness between moderately potent and potent topical corticosteroids were evident from the available data. A comparison of two potent preparations found some differences between the preparations in some outcomes (one trial). [EL = 1+] No evidence of the cost-effectiveness of different potencies of topical corticosteroids was identified.

Once-daily and twice-daily application of topical corticosteroids are both effective for the treatment of atopic eczema. It is not possible to distinguish between them on effectiveness or cost-effectiveness grounds. [EL = 1++]

Several studies reported changes in serum cortisol levels or responses to adrenal stimulation following topical corticosteroid treatment. It appeared that short-term use of topical corticosteroids of any potency did not cause statistically significant or clinically important suppression of adrenal function. In children treated with mild topical corticosteroids for several years, no evidence of adrenal suppression was found compared with a control group (one study). While

there was some suggestion that adrenal suppression could occur with potent topical corticosteroids, the available studies were not designed nor sufficiently powered to address what quantities or duration of use affected the risk of adrenal suppression. [EL = 3]

Other adverse effects reported with topical corticosteroids across the available studies included stinging on application, hypertrichosis, telangiectasia on cheeks, skin atrophy of antecubital or popliteal fossae, acne, folliculitis, bacterial infection, and steroid-induced and contact dermatitis. [EL = 3]

The single trial that compared a coal tar preparation with hydrocortisone 1% was of poor quality and did not allow any conclusions to be drawn. [EL = 1−]

From evidence to recommendations

The order in which emollients and topical corticosteroids should be applied is not known. Mixing creams and ointments may change the properties (formulation and absorption characteristics) of the treatments. The GDG therefore believes that a short interval (several minutes) should be left between application of a topical corticosteroid and an emollient, where practicable. [EL = 4] The GDG believes that treatments should be applied at times of day that are convenient to the child and their parents or carers. This could mean applying one dose of topical corticosteroid before school and one after school so that emollients are the only treatments needed at school.

It is the GDG's view that a short treatment with a potent topical corticosteroid is as effective as a longer treatment with a mild preparation. [EL = 4]

In children with frequent recurrent flares (two or three per month) of atopic eczema, the GDG believes that topical corticosteroids can be used for two consecutive days per week as a strategy for flare prevention. This is sometimes referred to as weekend therapy. This strategy can only be started once a flare has been controlled.

The risk of adverse effects due to topical corticosteroids is related to the surface area to which they are applied, the thickness of the skin, potency and duration of use. Therefore it is the GDG's view that treatment should be applied only to affected areas unless weekend therapy is being used in chronic persistent areas to prevent flares. The face and neck should only be treated with mild topical corticosteroids, apart from severe flares where topical corticosteroids of moderate potency can be used for up to 5 days. Moderately potent or potent topical corticosteroids can be used on other areas of thin skin such as the axillae and groin for 7–14 days only. [EL = 4]

The GDG believes that many healthcare professionals do not have enough specialist dermatological knowledge to recognise minimal signs of infection. Infection can be a cause of worsening or uncontrolled atopic eczema and it is important for healthcare professionals to consider infection before stepping up treatment to potent topical corticosteroids. [EL = 4]

Withholding topical corticosteroid treatment may lead to worsening of the child's atopic eczema, and deterioration in the child's quality of life. Adverse effects rarely occur when topical corticosteroids are used appropriately.

The GDG believes that topical corticosteroid preparations should be labelled with their potency group, and that this label should be applied to the container rather than the outer packaging to avoid confusion over potency, in order that the directions for use are not lost.

Recommendations for topical corticosteroids (including research recommendations) are presented in Section 7.11.

7.3 Topical calcineurin inhibitors

Pimecrolimus and tacrolimus are topical immunosuppressants. Pimecrolimus is derived from a fungus called *Streptomyces hygroscopicus* and tacrolimus is derived from *Streptomyces tsukubaensis*. Both pimecrolimus and tacrolimus bind to and inhibit the action of a protein called calcineurin, which is involved in the activation of T cells (one of the cell types that become activated in the skin of people with atopic eczema). They are therefore called calcineurin inhibitors. The main effect of calcineurin inhibitors is to inhibit the production of cytokines (chemical

messengers) produced by the T cells, which lead to the inflammation that produces flares of atopic eczema.

Topical tacrolimus ointment is available in two strengths: 0.03% and 0.1%. Only the 0.03% ointment is licensed for use in children, and this may only be prescribed for children aged 2 years or over. Pimecrolimus is a 1% cream that is licensed for use in children aged 2 years or over.

Overview of available evidence

NICE guidance on topical tacrolimus and pimecrolimus for the treatment of atopic eczema in children and adults was published in 2004.[13] The HTA that informed the NICE guidance included evidence for both children and adults.[291] Evidence that relates to children is summarised in this section, together with evidence published more recently. The HTA included the following RCTs in children:

- four RCTs evaluating topical tacrolimus (two compared with vehicle[292-294] and two compared with topical corticosteroids[265,266])
- three RCTs comparing pimecrolimus with vehicle (data from two are pooled in one report).[295-297]

The following additional studies have been published since the HTA:

- a systematic review of RCTs evaluating the efficacy and tolerability of topical pimecrolimus and tacrolimus in children and adults; this review was checked for references relevant to children with atopic eczema[298]
- RCTs of topical pimecrolimus 1% cream: four versus vehicle[110,299-304] (three with an extended follow-up period of open pimecrolimus use[299,301,303]), and one versus topical tacrolimus ointment 0.03%[305]
- pooled analyses of vehicle-controlled RCTs evaluating pimecrolimus 1% cream, which focused on specific outcomes or on response to treatment in specific patient groups[109,306]
- RCTs of topical tacrolimus 0.03% ointment: versus vehicle,[307] pimecrolimus 1%,[305] clobetasone butyrate 0.05% cream alone or in combination[267] and methylprednisolone[308]
- one cohort study within-patient (left–right side) comparison with usual topical corticosteroid treatment and tacrolimus 0.03% or 0.1%[309]
- five case series of tacrolimus 0.03% ointment [310] or 0.1%[311-314]
- Four case series of pimecrolimus 1% cream,[315-318] three of which specifically considered systemic absorption (blood concentrations).

Except for one RCT, all were funded by the manufacturers of the calcineurin inhibitors, and they tended to be of similar design, evaluating the same outcomes. Note that several studies were reported in more than one publication.

Pimecrolimus

Studies included in the HTA
The studies included in the HTA were vehicle-controlled double-blind RCTs evaluating pimecrolimus 1% cream in children aged 1–17 years, the majority aged 12 years or under. The first study report pooled outcome data for children with mild or moderate atopic eczema who were also treated with emollients from two identical RCTs (n = 403).[295] After 6 weeks' treatment there were significant differences in efficacy outcomes between the pimecrolimus 1% and vehicle groups:

- 35% versus 18% (pimecrolimus 1% cream versus vehicle) were clear or almost clear (IGA score of 0 or 1) of atopic eczema, $P \leq 0.05$
- severity scores (EASI) fell by 45% versus 1%, $P \leq 0.001$
- 55% versus 33% had a pruritus score of none or mild itching/scratching, $P < 0.001$
- 61% versus 40% of parents reported good or complete control of the child's atopic eczema, $P < 0.05$.

The effects of treatment on the quality of life of parents of children aged up to 8 years in this study were reported in a separate publication (n = 278). Data from 80% at 6 weeks showed significantly greater improvements in PIQoL-AD scores in the pimecrolimus 1% group compared with

vehicle (least squares mean change −3.2 versus −1.63, difference 1.57, 95% CI 0.22 to 2.92).[296] No significant differences were found in any of the reported adverse effects. Overall, 10.4% in the pimecrolimus group and 12.5% in the vehicle group had application-site reactions.[295] [EL = 1+]

The second RCT considered the effectiveness of pimecrolimus 1% cream in the prevention of flares in children with mild to moderate atopic eczema (n = 713).[297] Treatment with pimecrolimus or vehicle was applied at the first sign (erythema) or symptom (pruritus), to prevent progression to flare. A flare was defined as at least severe erythema and severe infiltration/papulation (IGA score of 4 or more). Emollients were used throughout the study by both groups, and both groups also applied a moderately potent topical corticosteroid during flares. Significantly fewer children experienced flares in the pimecrolimus 1% group at both 6 months (39% pimecrolimus versus 66% vehicle, P < 0.001) and 12 months (49% versus 72%, P < 0.001); relative risk (RR) of having a flare with pimecrolimus 1% compared with vehicle at 12 months 0.69 (95% CI 0.61 to 0.77). Fewer children treated with pimecrolimus used topical corticosteroids for flares than those receiving vehicle (43% versus 68%), and the mean proportion of days spent being treated with topical corticosteroids was 4% versus 9%. Of the adverse effects reported, no significant differences were seen between groups except in the incidence of viral infection (12.4% pimecrolimus versus 6.3% vehicle). More children withdrew from the vehicle arm (51.5% versus 31.6%), which was predominantly due to an unsatisfactory therapeutic response.[297] [EL = 1+]

Studies published since the HTA

The use of pimecrolimus 1% cream was evaluated in children aged 3–23 months in two vehicle-controlled double-blind RCTs of 4–6 weeks' duration.[110,299–301] Treatment was applied twice daily to affected areas. Emollients were permitted on unaffected areas throughout both trials.

One study found that, at 6 weeks, the proportions of children with IGA scores of clear or almost clear were significantly higher in the pimecrolimus 1% group (55% versus 24% with vehicle, P < 0.001). Improvements in severity (EASI score), the proportions of children with absent or mild pruritus, or with a carers' assessment of complete or good control were also significantly greater with pimecrolimus. Other than a significant difference in the incidence of pyrexia (32% pimecrolimus 1% cream versus 13% vehicle), there were no other differences in adverse effects between groups. The discontinuation rates in the pimecrolimus 1% and vehicle groups were 11% and 48%, respectively. [EL = 1+] Following the 6 week double-blind period, all children were offered treatment with pimecrolimus. Overall, 93% used pimecrolimus 1% cream for a further 20 weeks. The data suggested sustained benefit. All adverse effects reported in both groups were common childhood ailments (including pyrexia, nasopharyngitis and otitis media). Pyrexia was the only adverse effect that occurred in significantly different proportions in treatment groups (32% pimecrolimus 1% cream versus 13% vehicle, P < 0.05).[299] [EL = 3]

The second study reported significantly greater improvements in EASI, IGA and SCORAD scores in children treated with pimecrolimus 1% cream for 4 weeks compared with placebo (n = 196). There were no significant differences between groups in the change in the proportion of children with dry skin, or in adverse effects.[300,301] [EL = 1+] Quality of life outcomes at 4 weeks were reported in a separate publication (quality of life in parents of children with atopic dermatitis (PQoL-AD)). Significantly greater improvements in each of the five subscales were reported in those treated with pimecrolimus compared with vehicle (psychosomatic wellbeing, effects on social life, confidence in medical treatment, emotional coping, acceptance of disease).[110] Following the randomised phase of the study, children were offered pimecrolimus treatment for 12 weeks. During this time, improvements in efficacy outcomes were reported to be sustained although no numerical data were reported. Adverse effects believed to be related to treatment (which treatment was not specified) occurred in six children (two cases of impetigo, and one case each of eczema herpeticum, varicella, asthma, aggravated atopic eczema, and exacerbated eczema).[301] [EL = 3]

Two RCTs considered the effectiveness of pimecrolimus 1% cream compared with vehicle in the prevention of flares.[302–304] Emollients were used in both studies to treat dry skin. The first included children aged 3–23 months (n = 250).[302] The study was identical in design to one in older children described earlier.[297] Significantly fewer children experienced flares in the pimecrolimus group at 6 months (32% pimecrolimus 1% cream versus 70% vehicle) and at 12 months (43% versus 72%); the mean numbers of flares per child were 1.0 versus 2.2, P < 0.001. Fewer children treated with pimecrolimus 1% used topical corticosteroids for flares than those receiving vehicle

(36% versus 63%), and the mean proportion of days spent being treated with topical corticosteroids was 3% in the pimecrolimus group and 6% with vehicle (which corresponds to 11 days' use and 22 days' use, respectively). There were no significant differences between groups in the proportion with an IGA score of clear or almost clear, in severity (EASI) or pruritus scores or caregivers' assessment at 12 months. There were no significant differences in the incidence of the reported adverse effects (application-site reactions or skin infection).[302] [EL = 1+] Overall, 91 children (36%) continued into a second year of the study, applying pimecrolimus 1% for a median of 99 days. The data indicated sustained response to pimecrolimus 1% and no increase in incidence of adverse effects.[303]

A further RCT considered the effectiveness of pimecrolimus 1% cream in preventing progression of atopic eczema to flares in children aged 3 months to 11 years (n = 275).[304] Pimecrolimus 1% or vehicle was used at the first signs or symptoms of atopic eczema. If after 7 days' treatment with pimecrolimus or vehicle the child was believed to have a major flare, the evening dose of pimecrolimus 1% or vehicle was substituted with a potent topical corticosteroid. After 6 months' treatment, significantly more children in the pimecrolimus 1% group had not experienced a flare (52% versus 34% with vehicle, P = 0.007). Time to first flare and the median time between first and second flares were also significantly longer in the pimecrolimus 1% group. Mean duration of use of topical corticosteroids was 10.9 days with pimecrolimus 1% and 17.3 days with vehicle, P = 0.002. The withdrawal rate due to unsatisfactory therapeutic effect was significantly higher in the vehicle group (14.3% versus 3.8%, P = 0.003). Rhinorrhoea (runny nose) was the only adverse effect reported in significantly different proportions between groups (9.8% pimecrolimus 1% cream versus 2.2% vehicle, P = 0.025). Other reported adverse effects were predominantly respiratory or gastrointestinal.[304] [EL = 1+]

Quality of life data from two RCTs[297,302] that considered whether pimecrolimus 1% cream prevented flares have been published separately in a single report.[109] Both studies considered quality of life of parents of children aged up to 8 years (using PIQoL-AD), and one considered the quality of life of children aged 5 years or over (using CDLQI). Improvements in both measures were significantly greater with pimecrolimus 1% compared with vehicle.[109]

Pooled analysis of pimecrolimus versus vehicle studies

Data from three vehicle-controlled RCTs[295,299] were pooled in one report in order to consider the treatment effects in children of different ethnicities (n = 589). Children were subdivided into those of Caucasian origin (54%) and non-Caucasian origin (46%, of which 42% were black, 12% Asian, and 47% 'other', mainly Hispanic). No significant differences in treatment response (IGA and EASI scores) or in application-site reactions were found between children of Caucasian or non-Caucasian origin.[306] [EL = 1+]

Case series of pimecrolimus

A case series reporting the use of pimecrolimus 1% cream in children and adults with atopic eczema included some data for children aged under 2 years and those aged 2–12 years (n = 591 (62%) aged 2–12 years). Pimecrolimus 1% was applied to affected areas twice daily at the first signs or symptoms of atopic eczema. Other 'usual treatments' were permitted at the physician's discretion. Of all patients enrolled, 88% used emollients at baseline; 53% used a topical corticosteroid at least once during the study; and pimecrolimus was used for 75% of the time, and daily by 55%. In children, improvements in IGA whole-body and facial scores were reported in 66% and 78%, respectively, for those aged under 2 years, and in 71% and 79%, respectively, of children aged 2–12 years. The most common adverse effects (reported in more than 10% of children aged up to 12 years) were nasopharyngitis, upper respiratory tract infection, cough and pyrexia. Overall, 5.2% reported application-site burning, and 2% reported worsening of atopic eczema. Treatment-related adverse effects reported in children were five cases (0.8%) of eczema herpeticum.[315] [EL = 3]

Three case series measured blood concentrations of pimecrolimus following application of the 1% cream. The first found that, of 100 samples taken after 10 days' treatment, the blood concentration of pimecrolimus was below 2 ng/ml in 96%, and the difference in mean concentration between those with 90% and those with 10% of body surface area affected was 0.4 ng/ml (n = 22).[316] In the second study, the concentration of pimecrolimus was below 2 ng/ml in 98% of samples taken on days 4 and 22 of treatment. Results were in a similar range on days 4 and 22. The mean difference in blood concentrations between those with 90% and those with 10% of

body surface area being treated was 0.7 ng/ml; on linear regression analysis a significant increase in blood concentrations with increasing surface area was found, $P = 0.28$ ($n = 26$).[317] Five infants (6–12 months of age) from the latter study were followed up for 1 year, with a mean duration of use of pimecrolimus of 332 days. Mean blood concentrations were 0.32 ng/ml at week 27, and 0.68 ng/ml at week 53.[318] [EL = 3]

Tacrolimus

Studies included in the HTA

Four RCTs included in the HTA evaluated the use of tacrolimus 0.03% ointment in children.[265,266,292-294] Three of these also compared tacrolimus 0.03% ointment with higher strengths (0.1% and/or 0.3%) of topical tacrolimus.

One RCT compared 3 weeks' treatment with three strengths of topical tacrolimus ointment with vehicle in children aged 7–16 years ($n = 180$). Children were also permitted to use emollients on unaffected areas. All strengths of tacrolimus ointment (0.03%, 0.1% and 0.3%) led to significantly greater improvements in effectiveness compared with vehicle (physician's and patient's global evaluations, EASI, head and neck score, and pruritus). No significant differences in incidence of application-site reactions (burning, pruritus or erythema) were reported. Blood concentrations of tacrolimus appeared to increase with increasing strength of the ointment applied.[292] [EL = 1+]

Another RCT compared topical tacrolimus 0.03% and 0.1% ointment with vehicle in children with moderate to severe atopic eczema ($n = 351$).[293,294] Treatment was applied twice daily for up to 12 weeks, or less if the atopic eczema cleared sooner. Emollients were permitted on unaffected areas. Both strengths of tacrolimus ointment were significantly more effective than vehicle in all effectiveness outcomes (physician's and patient's global assessment, changes in EASI and pruritus scores, body surface area affected, and quality of life (CDLQI)). The incidence of skin burning, pruritus, varicella, and vesiculobullous rash was significantly higher with tacrolimus 0.03% ointment compared with vehicle.[293,294] Blood tacrolimus concentrations were measured: none was detected in 90%, and mean and median levels were below the limit of quantification (2 ng/ml) at all time points.[293] [EL = 1+]

One RCT compared the effectiveness of tacrolimus 0.03% ointment applied once or twice daily with hydrocortisone acetate 1% in children with moderate to severe atopic eczema ($n = 624$). Treatment was given for 3 weeks. Use of unmedicated emollients and bath oils was permitted. Tacrolimus 0.03% ointment (applied once or twice daily) was significantly more effective than hydrocortisone 1% in changes in severity scores (modified EASI (including assessment of itch) and EASI); twice-daily application of tacrolimus 0.03% ointment was also significantly more effective than once-daily application in this outcome. Analysis of between-group differences in physician's or parent's/child's global assessment, itch or sleep quality was not reported. The incidence of skin burning was significantly higher in both tacrolimus 0.03% ointment groups compared with hydrocortisone acetate 1% (23.2% with once-daily application of tacrolimus, 23.8% with twice-daily application, and 14.5% with hydrocortisone, $P = 0.028$). No other significant differences were found in the most commonly reported adverse effects (pruritus, folliculitis, influenza syndrome, skin infection).[265] [EL = 1+]

Another RCT compared the effectiveness of tacrolimus 0.03% and 1% to hydrocortisone acetate 1% in children with moderate to severe atopic eczema ($n = 560$). Treatment was applied twice daily for 3 weeks. Use of bath oils and unmedicated emollients was also permitted. Median improvements in modified EASI scores (including an assessment of itch) were significantly greater with both tacrolimus ointment groups compared with placebo, and with tacrolimus 0.1% versus 0.03% (55.2% tacrolimus 0.03%, 60.2% tacrolimus 0.1%, 36% hydrocortisone, $P < 0.001$ tacrolimus groups versus hydrocortisone and $P = 0.006$ tacrolimus 0.1% versus 0.03%). The proportion of children with a physician-rated improvement of 90% or more was significantly higher in both tacrolimus groups compared with hydrocortisone (38.5% tacrolimus 0.03%, 48.4% tacrolimus 0.1%, 15.7% hydrocortisone, $P = 0.001$ both tacrolimus ointment groups versus hydrocortisone and $P = 0.055$ between tacrolimus groups). Skin burning occurred in significantly more tacrolimus-treated children compared with hydrocortisone (18.5% tacrolimus 0.03%, 20.4% tacrolimus 0.1%, 7% hydrocortisone, $P < 0.05$ both tacrolimus groups versus hydrocortisone). No other significant differences in the incidence of adverse effects were reported (pruritus,

folliculitis, skin infection and skin erythema).[266] Blood concentrations of tacrolimus were measured. Overall, 1.3% of all measurements were 1 ng/ml or higher in those treated with tacrolimus 0.03%, compared with 11.3% in the group treated with tacrolimus 0.1%.[266] [EL = 1+]

Studies published since the HTA

One RCT compared tacrolimus 0.03% ointment with vehicle (both applied twice daily) in children with mild to moderate atopic eczema (n = 317).[307] Unmedicated emollients were permitted on unaffected areas. After 6 weeks' treatment, improvements in all efficacy outcomes were significantly greater in the tacrolimus group (IGA, body surface area affected, EASI and itch scores). Itching and erythema occurred in significantly more children treated with vehicle than tacrolimus (itching 23.4% versus 33.3%, P = 0.05; erythema 7.6% versus 18.9%, P = 0.003), and the withdrawal rate due to skin reactions was also significantly higher in the vehicle group (2.5% versus 7.5%, P = 0.04). There were no other significant differences in adverse effects reported (burning/stinging, folliculitis, skin infections, acne and eczema herpeticum).[307] [EL = 1+]

One RCT aimed at comparing application-site reactions between topical tacrolimus 0.03% ointment and pimecrolimus 1% cream in children with moderately severe atopic eczema.[305] Emollients were permitted on unaffected areas. At day 4, the proportions of application-site reactions were 26% with tacrolimus 0.03% ointment and 24% with pimecrolimus 1% cream. Erythema/irritation occurred in 19% versus 8% (P = 0.039), itching in 20% versus 8% (P = 0.073) and warmth/stinging/burning in 17% versus 20% (P = 0.931). Withdrawal rates were 4% with tacrolimus and 18% with pimecrolimus. No significant differences were reported in efficacy outcomes assessed at 6 weeks (proportions of children with IGA scores of clear or almost clear 42% versus 30%, P = 0.119; proportions of children with absent or mild pruritus 70% versus 64%, P = 0.493).[305] [EL = 1+]

One RCT compared tacrolimus 0.03% ointment with clobetasone butyrate 0.05% cream and with combined use of the two preparations in children aged 7–15 years with moderate to severe atopic eczema (n = 45).[267] Treatment was applied twice daily except in the combination group where tacrolimus was applied in the morning and clobetasone butyrate in the evening. Use of unmedicated emollients and bath oils was permitted. After 4 weeks' treatment, improvements in modified EASI scores and the reduction in body surface area affected were significantly greater with clobetasone butyrate than tacrolimus 0.03% ointment, and with combination therapy compared with tacrolimus ointment alone. No between-group analysis was reported for IGA. Differences in skin burning rates between groups were not statistically significant.[267]

One RCT compared 0.03% tacrolimus ointment with topical methylprednisolone in 265 children (mean age 7.5 ± 4.2 years tacrolimus, 7.8 ± 4.2 years methylprednisolone) with severe to very severe atopic eczema.[308] [EL = 1−] Children were randomised to either tacrolimus 0.03% ointment applied twice daily or methylprednisolone 0.1% in the evening over all affected areas for 2–3 weeks. Cleared areas were treated for an additional 7 days post clearance. At the end of the study, IGA and EASI scores and body surface area affected all showed significant improvement in both groups, with no statistically significant differences between the groups. Children's assessment of itch (P = 0.0004) and sleep (P = 0.0094) on a visual analogue scale were significantly better in the methylprednisolone group than in the tacrolimus group. The study also highlighted the difference in mean cost of the treatment used (tacrolimus 100.99 euros versus methylprednisolone 14.59 euros).

In a cohort study which used within-patient (left–right side of body) comparison, tacrolimus 0.03% or 0.1% ointment was compared with the child's usual topical corticosteroid treatment.[309] [EL = 2−] Ninety-six children (aged 12 years or under) with moderately severe atopic eczema were treated on one side of their body (arms and legs) with their usual topical corticosteroid and on the other side with tacrolimus 0.03% for 7 days. If the tacrolimus 0.03% had no effect in the first 7 days the dosage was increased to tacrolimus 0.1% for a further 7 days. After the first 7 days 48/93 children had a greater improvement with tacrolimus 0.03% compared with the topical corticosteroid as determined by clinical assessment of erythema and lichenification. The other 45 children were then given tacrolimus 0.1% for the same side of the body for another week. Over this second period of treatment 24/45 showed a more marked improvement compared with the usual treatment side. Thus, overall tacrolimus treatment (0.03% and/or 0.1%) showed greater improvement in 77% of the children treated compared with their usual topical corticosteroid.

Case series of tacrolimus

Four case series reported adverse effects in children and adults who had used topical tacrolimus over longer periods than evaluated in RCTs. The majority of patients used tacrolimus 0.1% ointment.[310-313] [EL = 3]

Three case series reported the most common adverse effects (occurring in 5% or more) in children aged 2–15 years who had been treated with topical tacrolimus for 6 months (n = 236, 35% were children),[311] 34 weeks (n = 3959 children)[310] and 16 months (n = 466 children).[313] Application-site effects were burning (19–38%),[310,311,313] pruritus (17–34%),[310,311,313] skin infection (15–32%),[310,311,313] paraesthesia (numbness 9%),[311] warmth (5%)[311] and skin erythema (5–7%)[310,313] [EL = 3]

The fourth case series provided data for children aged 2–15 years who were treated with tacrolimus 0.1% ointment for a median of 902 days (2.5 years; range 1–1186 days). The most common application-site events (occurring in 5% or more) were pruritus (21% in children aged 2–6 years and 19% in those aged 7–15 years), pustular rash (15.7% and 11.2%, respectively), skin burning (20.5% and 18.0%, respectively), skin erythema (10.8% and 5.8%, respectively) and skin infection (22.7% and 22.3%, respectively). The incidence of infections in children aged 2–5 years and those aged 7–15 years was herpes simplex 4.3% and 6.3%, respectively, warts 6.5% and 7.3%, respectively, varicella zoster 9.2% and 1.9%, respectively, molluscum contagiosum 3.2% and 4.9%, respectively, and eczema herpeticum 0% and 0.5%, respectively. Discontinuation rates due to adverse effects were 2.7% in children aged 2–6 years and 1.0% in children aged 7–15 years.[312] [EL = 3]

A fifth case series investigating the effect of tacrolimus 0.03% on moderate to severe atopic eczema in children (n = 58, mean age 6.98 ± 2.81 years) over a 4 week period showed a statistically significant improvement from baseline in the severity of the atopic eczema (EASI) and quality of life (CDLQI) ($P < 0.001$ and $P < 0.01$, respectively).[314] [EL = 3] Adverse events reported were similar to the other case series of longer duration and higher dose of tacrolimus, namely burning, erythema and itching.

Other relevant guidance

As well as NICE guidance, a Europe-wide safety review of the risks and benefits of topical tacrolimus and pimecrolimus ointments was completed in March 2006, following reports of malignancy (skin cancers, lymphomas and others) in association with the use of these two products.[319] The conclusion was that a causal link could not be determined. The UK Medicines and Healthcare products Regulatory Agency (MHRA) advised that:

- pimecrolimus 1% cream should be used as a second-line treatment for mild to moderate atopic eczema where treatment with topical corticosteroids is not possible or inadvisable
- tacrolimus ointment remains as a second-line treatment for moderate or severe atopic eczema in patients who do not have an adequate response to, or are intolerant of, topical corticosteroids
- treatment with pimecrolimus or tacrolimus should only be initiated by physicians experienced in the diagnosis and treatment of atopic eczema; they should not be given to patients with congenital or acquired immunodeficiencies, or to patients on therapy causing immunosuppression; and they should not be applied to malignant or potentially malignant skin lesions
- neither pimecrolimus 1% cream nor tacrolimus 0.03% ointment is licensed for use in children aged under 2 years
- in children the frequency of administration of tacrolimus 0.03% ointment should be limited to once daily
- the lower strength of tacrolimus should be used in adults wherever possible
- the products should be applied thinly and to affected areas of skin only
- treatment should be short term; continuous use should be avoided
- if no improvement occurs (after 6 weeks' pimecrolimus treatment or 2 weeks' tacrolimus treatment), or if the disease worsens, the diagnosis of atopic eczema should be re-evaluated and other therapeutic options considered.[319]

Evidence statement for topical calcineurin inhibitors

In short-term studies (4–6 weeks), pimecrolimus was more effective than vehicle alone in children with mild to moderate atopic eczema in terms of physician-reported measures of disease activity (including global assessment of disease activity, reduction in severity and itching), and improvements in quality of life of children and their parents. [EL = 1+] Intermittent application of pimecrolimus at the first sign or symptom of atopic eczema was more effective than continuous application of emollients in reducing the frequency of flares and the need for concomitant use of topical corticosteroids to treat flares, and in improving quality of life of parents and children. [EL = 1+] While most adverse effects reported occurred with similar frequency with pimecrolimus and vehicle, the incidence of viral infections, pyrexia and rhinorrhoea (runny nose), all of which are common childhood ailments, was significantly higher with pimecrolimus (one study each). Skin infections believed to be associated with pimecrolimus use included varicella, herpes simplex and eczema herpeticum. Application-site reactions were common with both pimecrolimus and vehicle, and not significantly different in overall incidence between pimecrolimus and tacrolimus (one study). [EL = 1+] No studies that compared pimecrolimus with topical corticosteroids were identified.

In short-term studies (3–12 weeks), tacrolimus 0.03% ointment was more effective than vehicle alone in children with mild to severe atopic eczema in terms of physician-reported measures of disease activity (including global assessment of disease activity, reduction in severity and itching) and improvement in children's quality of life. Twice-daily application of tacrolimus was more effective than once-daily application in reducing severity in children with moderate to severe atopic eczema (one study). [EL = 1+] Tacrolimus use was more commonly associated with skin burning, and greater skin erythema/irritation than pimecrolimus was (one study). [EL = 1+] Compared with a mild topical corticosteroid (hydrocortisone acetate 1%), tacrolimus 0.03% and 0.1% ointments were both more effective in reducing disease severity in children with moderate to severe atopic eczema. [EL = 1+] Differences between tacrolimus 0.03% and 0.1% were inconsistent. Evidence from one small trial suggested that short-term use of a moderately potent topical corticosteroid (clobetasone butyrate 0.05%) alone or in combination with tacrolimus 0.03% ointment was more effective than tacrolimus 0.03% ointment alone in reducing severity and body surface area affected by atopic eczema. [EL = 1+] There was a lack of data for tacrolimus compared with potent topical corticosteroids.

Cost-effectiveness

Studies included in the HTA

The HTA[291] that informed the NICE TA[13] reviewed the cost-effectiveness of tacrolimus and pimecrolimus for various severities of atopic eczema. Only one published cost-effectiveness analysis (which considered both costs and effectiveness simultaneously rather than costs alone) was identified in the HTA review.[320] This US study compared the cost-effectiveness of a course of tacrolimus with 2 week and 4 week courses of topical corticosteroids. The study was poorly conducted (it failed to use appropriate methods for calculating cost-effectiveness ratios) and so the cost-effectiveness analysis was recalculated in the HTA using data from the published study. The results showed that tacrolimus was dominant, that is it was both less costly and more effective than the 2 week course of topical corticosteroids, but the 4 week course of topical corticosteroids was more cost-effective than either tacrolimus regimen. The reported costs were modest (US$7 for tacrolimus, US$10 for the 2 week course of topical corticosteroids and US$7 for the 4 week course), but this was of very limited relevance in the context of the NHS.

Two economic models from pharmaceutical industry submissions were also reviewed in the HTA. The tacrolimus model did not measure benefits in QALYs, and the pimecrolimus model compared treatment with placebo only and thus was of very limited value.

A model was developed for the HTA to evaluate the cost-effectiveness of pimecrolimus and tacrolimus for children and adults in the UK. The pimecrolimus analysis was also reported separately in a subsequent publication.[321]

Eight Markov (state transition) models representing specific cohorts of adults and children (aged 2–16 years) were created. Each group was modelled separately in order to calculate

the costs and outcome values associated with that group. The four children's models were for those with:

- mild to moderate atopic eczema on the face only
- mild to moderate atopic eczema elsewhere on the body
- moderate to severe atopic eczema on the face only
- moderate to severe atopic eczema elsewhere on the body.

The treatment alternatives considered were:

- baseline standard treatment – topical corticosteroids only
- topical corticosteroids as first-line treatment, with pimecrolimus (for mild to moderate atopic eczema) and tacrolimus for moderate to severe atopic eczema as second-line treatments
- pimecrolimus (for mild to moderate eczema) and tacrolimus (for moderate to severe eczema) as first-line treatments, with topical corticosteroids as second-line treatment.

Cost data were derived from data for the NHS published in 2003. Cost of infections and out-of-pocket expenses were not included since there was no evidence that these would differ across the two arms of the trials. Outcomes were expressed in QALYs, with QALY weightings derived from decrements in IGA scores (0.86 for an average of 0–1 decrements or 'mild' disease, 0.69 for 2–3 decrements or 'moderate' disease, and 0.59 for 3–5 decrements or 'severe' disease).

The results showed that there were fewer benefits (QALYs) associated with using pimecrolimus for mild to moderate body and facial atopic eczema in children as first- and second-line treatment relative to topical corticosteroids alone, and that there were higher costs associated with pimecrolimus. Therefore topical corticosteroids were the most cost-effective option for children with mild to moderate disease.

For the treatment of children with moderate to severe body eczema, tacrolimus conferred some additional health benefits over topical corticosteroids, but with an incremental cost per QALY of around £9,000 as first-line therapy and £14,000 as second-line therapy. This appeared to indicate that tacrolimus is cost-effective (below the NICE threshold for cost-effectiveness of £20,000 per QALY). However, the authors reported that these results were highly sensitive to changes in assumptions in the model, meaning that the results are not very robust.

For the treatment of moderate to severe facial eczema, the additional cost per QALY of tacrolimus as second-line therapy compared with topical corticosteroids was around £36,000 and as first-line therapy it was dominated by topical corticosteroids (that is, it was both more expensive and had fewer benefits). The results were highly sensitive to changes in the model parameters, making it difficult to draw conclusions about the relative cost-effectiveness of the treatment options.

Additional probabilistic analyses were undertaken in the HTA by simulating 1000 trials of the three treatment options to assess the likelihood of any of them being cost-effective. These analyses all indicated that the probability of any treatment option being cost-effective was less than 50%, reflecting the considerable uncertainty of the results.

The NICE TA interpreted this evidence taking into account additional analysis undertaken by the manufacturers of tacrolimus and pimecrolimus. It concluded that the cost-effectiveness analyses undertaken by the HTA indicated similar outcomes for each of the treatment strategies and that the uncertainty of specific variables used in the models meant that the results of the economic analysis could not form the basis of their recommendation. The manufacturers' analyses did not change this decision. The NICE TA reported additional evidence submitted to the committee from clinical experts and concluded that, because of the higher cost of tacrolimus and pimecrolimus and the potential unknown long-term adverse effects of treatment with these products, the experts would not recommend either calcineurin inhibitor as first-line treatment.

Economic evaluations published since the NICE TA

An industry-funded Canadian study modelled the cost-effectiveness of pimecrolimus and topical corticosteroids.[322] The effectiveness data came from three industry RCTs that were not referenced in the cost-effectiveness study, but they included children. It was not possible to ascertain whether they were among the RCTs considered in the guideline (the patient numbers were different to those reported in the RCTs described above). Resource use was expressed in Canadian dollars and outcomes expressed as QALYs, with QALY weightings converted from the trial IGA scores (0.99,

0.92, 0.84 and 0.74 for IGA scores 1 to 4, respectively). The study concluded that pimecrolimus was a cost-effective option given a cost-per-QALY threshold of 50,000 Canadian dollars. The study had only limited value since the costs and QALY values were derived from outside the UK and the source of the effectiveness data could not be verified.

A more recent US study published in 2006 was also industry-funded and based on clinical data from an industry trial that compared pimecrolimus 1% with conventional therapy (emollients together with topical corticosteroids for flares) for the prevention of flares for 1 year in children and young people.[297] This study also used QALY weightings converted from IGA scores (0.98, 0.95, 0.88 and 0.72 for IGA scores 1 to 4, respectively). No modelling was undertaken, but the incremental cost-effectiveness ratio (ICER) of pimecrolimus versus conventional therapy was reported to be around $34,000 per QALY, concluding that it was likely to be a cost-effective option in the USA.

The results of the economic analysis suggest that topical corticosteroids could be a cost-effective option compared with pimecrolimus for mild to moderate atopic eczema on the face and body in children. The results also suggest that tacrolimus may be cost-effective compared with topical corticosteroids for more severe atopic eczema, but the results were not robust owing to the high level of uncertainty in the parameters used in the models. Because of the high cost of topical calcineurin inhibitors, more robust evidence of their effectiveness is required to determine their relative cost-effectiveness compared with other therapies.

From evidence to recommendations

Clinical trial data for topical calcineurin inhibitors published since the NICE TA was prepared provided additional evidence in support of the recommendations of the NICE TA. There was still a lack of data comparing topical calcineurin inhibitors with topical corticosteroids. The NICE guidance was adopted in this guideline.

It is the GDG's view that the main advantage of topical calcineurin inhibitors over topical corticosteroids is that topical calcineurin inhibitors do not cause adverse effects such as skin atrophy (thinning of the skin). This is particularly beneficial when treating delicate sites such as the face, where the skin barrier is very thin and the amount of topical corticosteroid that passes through the skin can be enough to cause atrophy. It should be noted that both tacrolimus and pimecrolimus can be used on thin skin.

The GDG believes that topical calcineurin inhibitors should not be used under occlusion without specialist advice because of the risk of increased absorption.

Recommendations for topical calcineurin inhibitors (including research recommendations) are presented in Section 7.11.

7.4 Dry bandages and medicated dressings (including wet wrap therapy)

Various types of dressings can be used in the management of atopic eczema, including dry wraps, wet wraps, occlusive and semi-occlusive dressings and medicated bandages (see Table 7.3). A polythene adhesive film impregnated with fludroxycortide is also available (Haelan® Tape).

Bandaging produces occlusion leading to increased absorption of topical preparations. Other effects may also occur, including antipruritic effects, cooling and skin protection.

A survey of 233 members of the British Society of Paediatric Dermatology in 2001/2002 (40% response rate) found wide variation in UK practice in relation to how wet wrap therapies were used.[323]

Studies considered in this section

The HTA of treatments for atopic eczema did not cover dry bandages or medicated dressings.[26] Other narrative reviews were checked for studies of any design.[234,324,325] Where available, controlled trials evaluating the effectiveness of dry bandages and medicated dressings in children with atopic eczema were considered for this section. Where RCTs were not available, studies of any design were considered.

Table 7.3 Dressings used in the management of atopic eczema

Type of dressing	Method used
Dry wrap dressings	Open-weave tubular bandage or crepe bandage used as a protective dressing, e.g. to keep greasy moisturisers in place.
Wet wrapping	Two layers of open-weave tubular bandage applied over topical preparations. The bottom layer is soaked in warm water, squeezed out and then put onto the skin over the topical preparation wet and the top layer is dry. They can be worn under nightwear or ordinary clothes and used during the day or night. Wet wraps are available in bandage form or garments.
Occlusive/semi-occlusive dressings	These include vapour-permeable films and membranes and hydrocolloid dressings. They can be used over topical preparations. Nappies, sleep suits and pyjamas may also have an occlusive effect and enhance skin penetration of topical preparations.
Medicated bandages	Cotton bandages impregnated with a variety of therapeutic substances such as tar or ichthammol. The bandages are usually applied over topical preparations in a spiralling and pleated fashion in the direction of venous return. A layer of self-gripping, elasticised, non-adhesive bandage is usually needed over the bandage (topical preparation) to keep it *in situ*. The bandages can only be used on the limbs. They cannot be applied to the trunk and face as they may tighten as they dry.

Overview of available evidence

Four RCTs[249,250,326,327] evaluated the effectiveness of wet wrap dressings applied over topical corticosteroids (fluticasone, hydrocortisone and mometasone). The comparator was emollient (vehicle) in one study[250] and conventional treatment (topical corticosteroids plus emollients without wet wraps) in the other three.[249,326,327] The safety of topical corticosteroids under wet wrap dressings was considered in a non-randomised controlled trial[328] and in three case series.[329–331]

A brief report on the use of fluticasone in the wet wrap method was also identified, which only included seven patients (three children). Severity (SCORAD) and cortisol levels were reported after 2 weeks' treatment, but the report generally lacked information about the patients, their condition and other treatments used. Therefore, it was not considered further.[332]

Occlusive and medicated dressings

No RCTs evaluating the effectiveness of dry bandages, occlusive or medicated dressings (including silver-impregnated silk bandages or dressings) in the treatment of atopic eczema in children were identified. The use of a hydrocolloid dressing on top of clobetasol propionate lotion (no strength specified) in children and adults with refractory atopic eczema was reported in one case series (n = 48). It was not clear how many children were included in the series (the age range was 7–69 years) and no results were reported separately for children. Therefore, the study was not considered further.[333] [EL = 3]

Topical corticosteroids versus vehicle under wet wrap dressings

One RCT evaluated the effects of 5 days' inpatient treatment with wet wrap dressings of mometasone furoate 0.1% or vehicle applied twice daily in children aged 2–17 years with an exacerbation of atopic eczema. Lesions had to be present on the insides of both elbows or the backs of both knees for entry to this left–right study. Outcomes considered were disease severity (SCORAD), transepidermal water loss and *S. aureus* colonisation. Changes in SCORAD scores were shown only in graphs, with no numerical data provided. Improvements were evident in both groups, although this was reported to be greater in those treated with mometasone (P < 0.01). There were no significant differences between groups in transepidermal water loss. No data were shown for *S. aureus* colonisation.[250] [EL = 1−]

Topical corticosteroids under wet wrap dressings versus conventional treatment

One RCT compared the effectiveness of hydrocortisone 1% ointment under wet wrap dressings with conventional treatment (emollient and hydrocortisone 1% ointment) in children with moderate to severe atopic eczema (SCORAD scores ≥ 15; n = 50 randomised, 45 analysed).[249] Wet wrap dressings were used for 24 hours a day for 1 week, then for 12 or 24 hours a day as

required for a further 3 weeks. It was not made clear whether wraps were used on the whole body. After 4 weeks' treatment, there was no significant difference between the two groups in changes in severity (SCORAD), the quantity of hydrocortisone 1% ointment used, or in the proportion of children who used a sedating antihistamine. Reductions in SCORAD scores of 55% and 59% were reported with wet wrap versus conventional treatment. Significantly more children treated with wet wraps used antibiotics compared with conventional treatment (22% versus 0%, $P = 0.05$). Nurse- and carer-rated improvements were not significantly different between groups (proportions 'much better' or 'better' 65% versus 59% (nurse rating) and 70% versus 64% (carer rating)). Significantly fewer carers considered that the wet wraps were easy to use compared with conventional treatment (39% versus 73%, $P = 0.036$). While no children withdrew from conventional treatment, five (22%) withdrew from the wet wrap group owing to non-adherence.[249] [EL = 1−]

The second RCT (a pilot study) also compared hydrocortisone 1% and emollients under wet wrap dressings with conventional treatment (emollient and hydrocortisone 1%) in children with atopic eczema affecting 30% or more of their body surface area ($n = 19$).[326] Wet wrap dressings were applied twice daily for the first week, then only at night for the second week. Both groups used only an emollient during the third week. It was not made clear whether wraps were used on the whole body. No significant differences were found between groups in changes in SASSAD severity scores (mean change −10.3 versus −15.7, 95% CI for the difference −18 to 2), or in quality of life (IDQoL mean change −2 versus −7, 95% CI for the difference −10 to 3; DFI mean change −2 versus −5, 95% CI for the difference −14 to 2). However, this small pilot study may have been underpowered to detect differences. The study reported that the mean 2 month cost to the NHS was approximately £19 for a child under 2 years and £11 for children aged 2–15 years. Improvements in sleep were noted in both groups, but no between-group analysis was reported. Two children from each group withdrew from treatment and it was assumed these were included in the analysis. Reasons for withdrawal were folliculitis and inability to attend follow-up in the group treated with wet wraps, and non-adherence and treatment failure in the control group. In total, there were two cases of folliculitis among those treated with wet wraps.[326] [EL = 1+]

One RCT considered the effectiveness of wet wrap dressings using mometasone furoate 0.1% and fluticasone propionate 0.005% ointments, both diluted to one-tenth their strengths, compared with continued treatment with the same preparations without wet wrapping.[327] Children with moderate to severe refractory atopic eczema were enrolled ($n = 40$; 27 completed treatment and were analysed). Treatment was applied once a day over a 4 week period without wet wraps, or for 2 weeks without wet wraps followed by 2 weeks of application under wet wraps. It was not made clear whether wraps were used on the whole body. While reductions in disease severity score were noted for each group, no between-group comparisons were reported, nor were differences in baseline values accounted for. Disease extent scores fell significantly in both wet wrap groups (this outcome was not evaluated in the standard treatment group). Subjective assessment of disease impact on daily life was significantly reduced with the mometasone wet wrap, but not with the fluticasone wet wrap; again no between-group analysis was reported.[327] [EL = 1−]

Studies of other designs that considered adverse effects

The first report of the wet wrap technique was published in a letter. Children aged 9 months to 16 years were treated with hydrocortisone 0.5% ointment or a 10% dilution of betamethasone valerate 0.01% under wet wraps for 2–5 days. Suppression of serum cortisol levels was evident in all children during treatment but returned to normal 2 weeks later ($n = 30$).[334] [EL = 3]

A non-randomised controlled study focused on the effects of 2 weeks' treatment with various dilutions of fluticasone propionate 0.05% under wet wraps on serum cortisol levels ($n = 31$ children aged 5 months to 13 years).[328] However, data were poorly reported, with some presented only in graphs and with selective reporting of numerical data. While the authors claimed that the data suggested that weaker corticosteroid dilutions are associated with lower risk of hypothalamic–pituitary–adrenal (HPA) axis suppression, this was not evident from the data reported. Similarly, while disease severity was also measured, incomplete data were reported. Folliculitis was reported in 42%.[328] [EL = 2−]

Three case series involving a total of 36 children also measured early-morning serum cortisol levels in children treated with topical corticosteroid therapy under wet wrap dressings. In the

first case series, mometasone furoate 0.1% (diluted to 10% or 15% with emulsifying ointment) was applied once daily under wet wrap dressings for 2 weeks (*n* = 12). Early-morning plasma cortisol was measured in two-thirds of the children, with a result below the lower limit of the usual range recorded for one child. However, no baseline data were provided for comparison with this result. Folliculitis and a 'tight sensation' were reported as adverse events by 25% of children.[330] [EL = 3]

The second case series found that SCORAD severity scores decreased significantly from baseline after 9 days' treatment with fluticasone propionate 0.05% under wet wrap dressings in children and adults with refractory atopic eczema (*n* = 26, 14 children). Overall median serum cortisol levels fell significantly from baseline to day 7, but none of the values were below the lower end of the reference range (200 nmol/l).[329] [EL = 3]

The third case series measured lower leg length and urinary excretion of deoxypyridinoline crosslink as markers of growth and bone turnover in children treated with wet wrap dressings (*n* = 8).[331] Diluted beclometasone dipropionate (10% or 25%, in seven children) or emollient (one child) was applied under wet wrap dressings for 24 hours a day for 2 weeks, followed by overnight use for 1 week and then 'as required'. After median follow-up of 12 weeks (range 2–18 weeks), lower leg length velocity rates and bone turnover did not appear to be different from baseline values.[331] [EL = 3]

Evidence statement for dry bandages and medicated dressings (including wet wrap therapy)

RCTs evaluating the use of topical corticosteroids under wet wrap dressings were generally of poor quality. The results for treatment given over 2–4 weeks were conflicting, with no clear evidence of a difference in effectiveness (measured by disease severity and/or quality of life) between wet wrap and conventional treatment with topical corticosteroids plus emollients. The one RCT that compared wet wraps over topical corticosteroid versus vehicle did not provide sufficient information to enable conclusions to be drawn. [EL = 1−]

Use of wet wrap therapies was associated with higher use of antibiotics and higher withdrawal rates in one study. [EL = 1−] Folliculitis was reported in 20–42% of children across several studies. Carers found that wet wrap treatment was less easy to apply than conventional treatment. [EL = 3]

Up to 2 weeks' use of topical corticosteroids under wet wrap dressings did not appear to affect children's growth or bone turnover, although these data were derived from small studies. Reports of suppression of serum cortisol levels after 2–5 days' use have been documented. [EL = 3]

There was an absence of evidence regarding the effectiveness of dry bandages, medicated and occlusive dressings for the treatment of atopic eczema in children.

Cost-effectiveness

No cost-effectiveness studies of dry bandages or medicated dressings, including wet wrap dressings, were identified.

From evidence to recommendations

The GDG found no evidence that wet wrap therapy was more effective or cost-effective than conventional treatment for mild to moderate atopic eczema, but this may reflect the power and quality of the available studies. It is the GDG's view that wet wrap treatment with a topical corticosteroid can be beneficial in some cases, such as severe atopic eczema, very dry skin, flares that are not controlled by conventional topical corticosteroid application and limbs that are heavily scratched at night. The risk of systemic adverse effects from topical corticosteroids increases under occlusion and is proportional to the body surface area being treated. Therefore the duration of wet wrap treatment over topical corticosteroids should be limited to 7–14 days. [EL = 4]

Recommendations for dry bandages and medicated dressings (including research recommendations) are presented in Section 7.11.

7.5 Antihistamines and other antipruritics

There are a number of treatments available for severe pruritus and these include antihistamines and other antipruritics such as coal tar and bath oil preparations. Coal tar has been widely used in the past as a treatment for chronic atopic eczema. Antihistamines block the activity of histamine at receptor sites in the skin (predominantly H1 receptors), which alleviates itching and reduces the wheal and flare response, hence reducing urticaria. The relative antipruritic, anti-urticarial and sedative effects of antihistamine drugs vary.

Antihistamines are classified according to their sedative properties. Sedating antihistamines (also referred to as first-generation antihistamines) such as alimemazine (formerly known as trimeprazine), chlorphenamine (formerly known as chlorpheniramine), clemastine, cyproheptadine, hydroxyzine and promethazine act non-selectively, and tend to be shorter-acting (6–12 hours). Non-sedating antihistamines (also referred to as second-generation antihistamines) such as cetirizine, levocetirizine, loratadine, desloratadine and fexofenadine bind more selectively to peripheral histamine H1 receptors, although sedation can still occur. They have a longer duration of action (about 24 hours), except in infants where the drug may be metabolised more rapidly.

Studies considered in this section

The HTA of treatments for atopic eczema was checked for evidence relating to children.[26] Where available, RCTs evaluating the effectiveness of antihistamines or other antipruritics (coal tar, bath oil preparations and/or others) in children with atopic eczema were considered for this section. Where RCTs were not available, studies of any design were considered.

Overview of available evidence

RCTs evaluating the use of cetirizine, chlorphenamine, clemastine, cyproheptadine, hydroxyzine, ketotifen and loratadine in children with atopic eczema were identified. No trials of any design considered the effects of preparations containing coal tar on pruritus. One study compared the effects of two different coal tar 1% preparations in individuals (mostly children) with atopic eczema, but in terms of global improvement and patient preference rather than pruritus.[335] An RCT compared the effectiveness of an aqueous lotion containing sodium cromoglicate 4% with placebo in children with atopic eczema.[336] A study that investigated the use of a non-proprietary preparation of sodium cromoglicate used specifically for the study was not considered to be relevant to UK clinical practice and was not considered further.[337]

Antihistamines for the treatment of pruritus associated with atopic eczema

Cetirizine:
One double-blind placebo-controlled randomised trial considered the effectiveness of cetirizine in the treatment of mild to moderate pruritus in children aged 6–12 years with atopic eczema (n = 22).[338] The dosage of cetirizine given was dependent on body weight: 5 mg/kg daily was given to those weighing 30 kg or less, and 10 mg/kg daily to those over 30 kg. After 8 weeks' treatment there were significant differences between the two groups in terms of clearance of all signs and symptoms of atopic eczema (73% cetirizine versus 18% placebo, $P < 0.02$), and in use of concomitant therapy (disodium cromoglicate or topical corticosteroids: 18% cetirizine versus 82% placebo, $P < 0.01$). Severity of pruritus and erythema was also measured in the study, but no numerical results were reported.[338] [EL = 1+]

Chlorphenamine:
One double-blind RCT compared the effectiveness of chlorphenamine with placebo in children aged 1–12 years who had nocturnal itching and scratching associated with atopic eczema (n = 151).[339] Treatment was given for 4 weeks. The dosage of chlorphenamine given was 1 mg once daily for children aged 1–5 years and 2 mg once daily for children aged 6–12 years. Where itching was not reduced by the initial dose, a second identical dose was permitted from 3 hours after administration of the first dose. If itching had not improved at the end of the first 2 weeks of treatment then the dosage was doubled (2 mg and 4 mg for children aged 1–5 years and 6–12 years, respectively). Use of emollients and hydrocortisone 1% was permitted during the trial.[339]

After 4 weeks' treatment, no significant differences were identified between groups in any outcome. Severity of itching (graded on a five-point scale) was not significantly different between the two treatment groups: 56% in both groups had no itching, and 33% from the chlorphenamine group versus 29% from the placebo group reported minimal itching ($P = 0.745$). There was no significant difference between groups in terms of other outcomes assessed (investigator's rating of intensity of signs and symptoms, quantities of emollients or hydrocortisone use). Overall, 13% reported a total of 29 separate non-serious adverse events; no further details were reported.[339] [EL = 1+]

Hydroxyzine versus cyproheptadine:
One double-blind RCT evaluated the effects of hydroxyzine and cyproheptadine on pruritus (day and night) in children aged 2–16 years (mean age approximately 8 years) with an acute exacerbation of atopic eczema ($n = 20$).[340] The doses taken were 1.25 mg/kg three times daily (t.d.s.) of hydroxyzine (up to 30 mg t.d.s.), and 0.25 mg/kg t.d.s. cyproheptadine (up to 6 mg t.d.s.). The doses used were higher than those generally used in UK practice. The children were also using an emollient preparation three times daily, but no other medications were permitted. Improvement in both day and night pruritus was significantly greater with hydroxyzine than cyproheptadine after 7 days' treatment (mean improvement in daytime pruritus 32% versus 6%, $P < 0.001$; nighttime pruritus 48% versus 30%, $P < 0.005$). Physician-rated improvement of the severity of the condition at endpoint was also significantly greater in the hydroxyzine group. Other than sedation, noted in two children in the hydroxyzine group and three in the cyproheptadine group, no adverse effects were reported.[340] [EL = 1+]

Clemastine versus ketotifen:
A double-blind RCT compared the effectiveness of clemastine and ketotifen in children (mean age 9 years) with atopic eczema ($n = 284$ randomised, 255 analysed).[341] After 4 weeks' treatment, the proportion of children whose condition was moderately improved based on the investigator's rating was significantly higher with ketotifen; no other differences in the other six ratings were noted. In terms of individual symptoms, improvement in itching, erythema/papule and excoriation/scratch was found in significantly more children treated with ketotifen (itching 79% versus 57%, erythema/papule 73% versus 58%, excoriation/scratch 70% versus 54%). Other than the proportions reporting adverse events, which were similar in the two groups (clemastine 13% versus ketotifen 10%), details of adverse events were lacking.[341] [EL = 1−]

Loratadine versus placebo:
A study evaluating the use of loratadine in conjunction with topical mometasone furoate 1% cream in children with atopic eczema was identified ($n = 50$). Although the volume (and not strength) was reported in the paper, it was assumed that the only available proprietary preparation of loratadine was used (5 mg/5 ml). The dose given was 5 ml for children who weighed up to 30 kg, and 10 ml for those weighing more than 30 kg. After 15 days' treatment, there were no significant differences between groups in any outcome (improvement in severity (SCORAD) scores, physician's assessment of global improvement or pruritus score). Dizziness was reported by one child in each group; there were no reports of drowsiness or difficulty in awakening.[342] [EL = 2+]

Antihistamines used preventatively in children with atopic eczema
The Early Treatment of the Atopic Child (ETAC) study considered whether cetirizine could prevent the onset of asthma, and also provided longer term safety data for cetirizine. In this double-blind RCT, 18 months' treatment with cetirizine was compared with placebo in children aged 12–24 months with active atopic eczema ($n = 795$).[343–346] The dosage of cetirizine given was 0.25 mg/kg twice daily. Both groups were permitted to use topical or systemic medication if required.

There was no difference in cumulative prevalence of asthma between active and placebo groups after 18 months of treatment (38%). The proportion of children who reported one or more episode of urticaria was significantly lower with cetirizine (5.8%) than placebo (16.2%, $P < 0.001$).[343,346] There were no significant differences between the two treatment groups in the proportions who used topical preparations, or in the duration of their use (emollients, corticosteroids, nonsteroidal anti-inflammatory creams, 'tar', antibiotic/antiseptics) or systemic oral antibiotics. The quantities of other medications taken were not reported.

In the subgroup of children with more severe atopic eczema (SCORAD score of 25 or more; 44%), the mean percentage days' use of moderate to potent topical corticosteroids was significantly lower in the cetirizine group (25.8% cetirizine versus 35.1% placebo, representing 51 fewer days' use of such topical corticosteroids during the total trial period, $P = 0.014$). Despite the difference in topical corticosteroid use, overall reduction in disease severity scores (SCORAD) did not differ significantly between groups (change from baseline −39% cetirizine versus −37% placebo).[343] The proportion of children in the cetirizine group who were given other oral antihistamines was significantly lower than in the placebo group (18.6% versus 24.9%, $P = 0.03$). The mean percentage days of their use was also reported to be statistically significantly lower in the cetirizine group compared with placebo (3.4% versus 4.4%, $P = 0.035$), although the difference of 5 days over 18 months was not clinically important.[343] [EL = 1++]

There were no significant differences between the cetirizine and placebo groups in terms of rates of serious symptoms and adverse events (9.3% cetirizine versus 13.6% placebo, $P = 0.053$), or hospitalisation (9% cetirizine versus 11.8% placebo, $P = 0.189$). Similarly, there were no significant differences between groups in neurological symptoms or events, including insomnia, fatigue, somnolence, hyperkinesis, nervousness, emotional lability or febrile convulsions. Electrocardiogram and laboratory test results in both groups were within normal limits.[344]

Assessments of behaviour and psychomotor development were undertaken in some children (41% and 20%, respectively). There were no significant differences between groups in mean scores on the behavioural screening questionnaire or in psychomotor development scores measured by the McCarthy test.[344,345] [EL = 1++]

Sodium cromoglicate

A double-blind RCT compared the effectiveness of an aqueous lotion containing sodium cromoglicate 4% with placebo (lotion base only) in children with moderate to severe atopic eczema ($n = 114$, age range 2–12 years).[336] Treatment with emollients and topical corticosteroids continued as usual during the study. After 12 weeks, the severity of the atopic eczema (SCORAD score) was reduced by 36% (13.2) using sodium cromoglicate 4% compared with 20% (7.6) using placebo (mean difference 5.6, 95% CI 1.0 to 10.3). Further analysis comparing clinically relevant treatment success (defined as a reduction in SCORAD of at least 25% without an accompanying increase in topical corticosteroid use) showed that treatment with sodium cromoglicate 4% and placebo was associated with treatment success in 50% and 30% of children, respectively (OR 2.29, 95% CI 1.06 to 4.94). [EL = 1+]

Evidence statement for antihistamines and other antipruritics

Controlled trials evaluating antihistamines and other antipruritics for atopic eczema in children were few in number and generally evaluated short-term use (1–8 weeks' treatment) in relatively small numbers of children. The indications for treatment with an antihistamine were not always made clear. One large and longer study showed no difference in the use of topical corticosteroids between children taking cetirizine and those taking placebo. Where antihistamines were used to treat itching associated with atopic eczema in children, the available data were conflicting; there was no evidence that cetirizine or chlorphenamine led to greater improvements in pruritus compared with placebo. There was some evidence from one small trial that hydroxyzine was more effective than cyproheptadine in relieving pruritus over a period of 1 week. [EL = 1+] The RCT comparing ketotifen and clemastine was of poor quality which did not allow conclusions to be drawn. [EL = 1−] None of the studies considered the impact of antihistamine treatment on the children's or families' sleep or quality of life. No studies evaluated the use of sedating antihistamines for sleep disturbance in children with atopic eczema.

Cetirizine was as well tolerated as placebo in an 18 month trial evaluating its use for the prevention of asthma in young children with atopic eczema. In children with more severe atopic eczema (SCORAD ≥ 25), cetirizine reduced the use of moderately potent and potent topical corticosteroids. [EL = 1++]

Details of adverse effects were generally lacking across the studies that evaluated antihistamines for the treatment of atopic eczema, although none reported clinically important differences between antihistamines and placebo groups.

An RCT showed that treatment with an aqueous lotion containing sodium cromoglicate 4% was more effective than placebo (lotion base only) in reducing the severity of atopic eczema in children. [EL = 1+]

Cost-effectiveness

No published economic evaluation studies were identified. Antihistamines are not expensive treatments; some have shown some beneficial effects in treating atopic eczema in children, and these prescriptions are likely to be cost-effective. Sedating and non-sedating antihistamines cost about £5 to £10 per month (excluding outliers) (BNFC 2007).[232] Although no economic analysis was reported, the likelihood is that this is a cost-effective treatment in the circumstances for which it is recommended.

The ETAC trial[343] showed that children with atopic eczema given cetirizine used less topical corticosteroid and had a lower rate of urticaria than those treated with placebo. The reduction in treatment costs (not having to treat urticaria) may well have offset the initial (low) cost of the antihistamine, but the study did not report this. Without overall quality of life information, it was not possible to evaluate whether any additional cost of treatment was offset by the reduced costs and increased quality of life in reducing rates of urticaria.

From evidence to recommendations

The GDG's view was that antihistamines can be helpful in some circumstances (for example, when treating children with atopic eczema involving an element of urticaria), and that these treatments are likely to be cost-effective. Although the evidence base was poor, clinical experience still supports short-term (7–14 days) use of sedating antihistamines in children with atopic eczema that causes debilitating sleep disturbance to them or their families or carers. If treatment with sedating antihistamines is successful, it can be repeated during flares if needed. Non-sedating antihistamines can be used for 1 month in the first instance if there is severe itching or urticaria. This trial can be continued if successful but should be reviewed every 3 months. The GDG noted that all antihistamines can alter mood and cognitive function and long-term use should be avoided.

One RCT has shown that treatment with an aqueous lotion containing sodium cromoglicate 4% is effective in reducing the severity of atopic eczema in children. However, the treatment is not licensed for use in the UK and the GDG has, therefore, not recommended its use.

Recommendations for antihistamines and other antipruritics (including research recommendations) are presented in Section 711.

7.6 Treatment for infections associated with atopic eczema

Bacterial and viral infections that occur secondarily to atopic eczema, and their signs and symptoms, are:

- *Staphylococcus aureus* – increasing erythema, pustules or purulent exudation with crusting
- *Streptococcus pyogenes* (group A streptococcus) – similar to *S. aureus*
- eczema herpeticum (due to herpes simplex virus*)* – vesicles, punched-out erosions and pustules (often difficult to identify owing to accompanying impetiginisation)
- varicella (chicken pox) – generalised pruritic rash, mainly on trunk and face and less on distal limbs
- molluscum contagiosum – small, pearly-white or flesh-coloured umbilicated papules, which may be inflamed, with or without suppuration (pus) when about to involute (disappear)
- verrucae vulgaris (viral warts) – discrete papules with irregular frondy rugose surface.

Damage to the epidermal skin barrier from inflammation and scratching allows bacterialcolonisation, particularly with *S. aureus,* which represents about 90% of the total aerobic bacterial flora of people with atopic eczema; this compares to 30% in unaffected individuals.[26] Heavy colonisation of the skin with *S. aureus* has been reported in people with atopic eczema even when the skin is not clinically infected, and this may contribute to continuing disease activity.[347–349] The density of *S. aureus* tends to increase with the clinical severity of atopic eczema lesions.[350-354]

Serous exudate encourages bacterial growth and frequently leads to clinical infection (impetiginised eczema). This is associated with increased inflammation, heavy yellowish crusting and sometimes pustules and even frank blisters of impetigo, which can spread rapidly. The role of *S. aureus* in non-clinically infected atopic eczema skin or borderline infection is far from clear.[26]

In people with atopic eczema, a high rate (73%) of self-contamination from *S. aureus* carrier sites (nose, subungual spaces (under the nails), axillae (armpits), groin and the periauricular area (ears)) or from colonised skin lesions has been described.[355-357] Bacterial transmission between children with atopic eczema and family members has also been reported.[358-361]

Staphylococcus aureus can produce enterotoxins (enterotoxins A–E and toxic shock syndrome toxin-1).[362] These cause a number of diseases, some of which may be followed by fever and shock. The toxins can act as superantigens interacting with immune cells to induce or enhance inflammation of the skin (and other sites).[363] There is some evidence to suggest that the density of *S. aureus* is more important that the presence of superantigens in aggravating atopic eczema lesions.[364] Superantigens can also induce glucocorticosteroid insensitivity, which may increase the severity of atopic eczema.[362]

Severe atopic eczema associated with severe recurrent infections, especially deep abscesses or pneumonia, should be investigated as it may be associated with rare diseases such as Job syndrome, Netherton syndrome, Wiskott–Aldrich syndrome, and selective IgA deficiency.

Increased infection rates are associated with the use of immunosuppressive agents (such as corticosteroids) for the management of atopic eczema.

Eczema herpeticum (Kaposi's varicelliform eruption) is a generalised vesicular eruption caused by the herpes simplex (cold sore) virus (usually type 1). It is relatively uncommon, considering that both atopic eczema and recurrent herpes simplex occur in about 20% of the population. It has been suggested that children with atopic eczema are no more likely to acquire herpes simplex infections than are children unaffected by atopic eczema.[365] However, another study reported that adults who had had atopic eczema between the ages of 0 and 14 years had a greater incidence of recurrent herpes simplex infections than did non-atopic controls.[366]

Other viral infections such as varicella (chicken pox) may occasionally be very widespread in atopic eczema, mimicking eczema herpeticum.[367]

While infection with other organisms such as viral warts, including molluscum contagiosum, was once thought to be more common in people with atopic eczema, there is no evidence to support this.[368] Such organisms may, however, be more widespread or persistent because of scratching and/or the use of immunosuppressive therapies such as topical corticosteroids and topical calcineurin inhibitors.

Pityrosporum ovale and tinea (ringworm) infections are no more common in children with atopic eczema than other children.[369,370] Using topical corticosteroids can alter the clinical appearance of tinea infections, allowing low-grade spread of the causal fungus.

Yeast fungi (mainly *Candida* spp. and *Rhodotorula* spp.) are thought to be present on the skin of approximately 40% of people with atopic eczema. They are difficult to eliminate and can aggravate the course of the disease.[371]

Other itchy skin conditions such as scabies (infestation with *Sarcoptes scabiei* var. *hominis*) may coexist or be confused with atopic eczema. Scabies worsens the usual itching associated with atopic eczema and this usually results in considerable impetiginisation, which can mask the signs of scabies.

7.6.1 Identification of infections

Studies considered in this section

Most of the literature on skin infection in association with atopic eczema relates to *S. aureus,* although other microorganisms are associated with infected atopic eczematous skin. The studies considered in this section describe bacterial infections (n = 14) and viral infections (n = 28). No relevant studies were identified for *Pityrosporum ovale*, tinea, yeast fungi or scabies infections.

Overview of available evidence

Bacterial infections

Staphylococcus aureus alone:
Staphylococcus aureus infection associated with atopic eczema was described in one case series[372] and eight case reports of extremely rare complications caused by *S. aureus*.[373–376] [EL = 3]

The case series reported 22 secondary infections (31.4%) with *S. aureus* in 57 children with atopic eczema (severity mild to severe) aged 4 months to 14 years followed for an average of 4.73 months.[372] [EL = 3]

Four of the case reports described children under 12 years of age with severe atopic eczema and a confirmed *S. aureus* infection. All children exhibited pustules in the affected areas and one child had pustules and impetigo.[373] Two of the case reports described *S. aureus* septicaemia as a complication of infected atopic eczema in an infant and a 3-year-old child.[374] One case report described *S. aureus*-induced osteomyelitis associated with cutaneous colonisation of *S. aureus* in 4-year-old boy.[375] The third case report described a 3-year-old boy with severe atopic eczema and history of recurrent skin infections who was admitted to hospital with skin sepsis. Acute bacterial endocarditis was diagnosed as a result of *S. aureus* infection. Following treatment for his condition, the boy had two further episodes of septicaemia due to *Proteus mirabilis* and *Pseudomonas aeruginosa*.[376]

Staphylococcus aureus with streptococcus species:
Staphylococcus aureus complicated with streptococcal infections and atopic eczema were described in three case series[377–379] and one case report.[380] [EL = 3]

The first case series reported on 190 children (aged 7 weeks to 17 years, median age 3 years) with atopic eczema (no details of severity were reported) attending a hospital clinic and studied for a mean of 13 months.[377] [EL = 3] Seventy-six children (40%) had exacerbations of atopic eczema due to bacterial infections and in 52 (32%) infection recurred within 3 months. Twenty-five cases (15%) led to hospital admission. *Staphylococcus aureus* was recovered in 97% of cases and in combination with beta-haemolytic streptococci in 62%.

The second case series described 174 cases of streptococcal impetigo associated with atopic eczema, of which 112 were in children under the age of 14 years.[378] [EL = 3] The most frequent infectious agents were group A streptococci (71% *Streptococcus pyogenes*) followed by group G (19.5%) and group B (9.8%) *Streptococcus agalactiae*. Streptococci were isolated as sole pathogens in 28% of cases and in the remaining cases they were co-infecting with *S. aureus*.

In the third case series, six of 36 children under the age of 12 years with atopic eczema were found to have lesions infected with streptococci in addition to *S. aureus*.[379] [EL = 3] There were two cases of *Streptococcus pyogenes*, three cases of streptococcus group G, one of which also involved *Streptococcus agalactiae*, and one other unidentified streptococcus.

Two further case reports describing unusual infections were not considered to be relevant to the clinical management of atopic eczema.[380,381] [EL = 3]

Viral infections

Eczema herpeticum:
Eczema herpeticum was described in six case series[382–387] and nine case reports.[388–396] [EL = 3]

Eczema herpeticum may arise in normal-looking skin without evidence of active atopic eczema and sometimes in people who have not had active atopic eczema for many years. Lesions are all at the same stage of evolution. They start as small, grouped, circular blisters which often show a central depression (umbilication). They are all remarkably similar in size and appearance but quickly become eroded and crusted and often confluent in some areas. Transmission is by direct contact with infected secretions. The severity of eczema herpeticum ranges from localised disease to widespread dissemination and very rarely herpetic encephalitis and death. Mortality rates for untreated eczema herpeticum have been reported to be 6–10%.[387] The cause of death, though not always clear, may have been an undetected immune deficiency state such as Wiskott–Aldrich

syndrome or a secondary bacterial infection with *S. aureus* and streptococcus species. Repeated attacks do occasionally occur and should prompt a search for underlying immune deficiency.

Varicella:
Infection with varicella (chicken pox) was described in one case–control study.[397] [EL = 2–]

In otherwise healthy children with varicella infections, systemic symptoms are usually mild and complications are rare. In immunologically compromised children and children on steroid therapy, the infection is more likely to be associated with an extensive eruption, high fever, pneumonia and life-threatening complications.[397] In a case–control study comparing 32 children with atopic eczema and a varicella infection with 34 children with a varicella infection but no atopic eczema 37.5% (controls 5.9%) had persistent fever, 31% (5.9%) had profuse eruptions, and 87.5% (17.6%) had severe pruritus. [397] [EL = 2]

Viral warts:
Viral warts were described in one case–control study.[368] [EL = 2+] Infection with verrucae vulgaris was described in one case report.[398] [EL = 3]

Viral warts have traditionally been thought to be more common in children with atopic eczema than unaffected children. However, no evidence was identified to support this. In fact, one case-control study reported that warts were noted less frequently in children with atopic eczema than unaffected children at age 11 years and 16 years. [368] [EL = 2+]

Molluscum contagiosum:
Molluscum contagiosum was described in two case series[399,400] [EL = 3] and eight case reports.[401-403] [EL = 3] No evidence was identified to suggest that molluscum contagiosum was any more common in children with atopic eczema than in other children.

7.6.2 Antimicrobial agents

Treatments for infected atopic eczema involve the use of systemic antibiotics active against *S. aureus*, topically applied antibiotics, and antiseptic agents applied directly to the skin or mixed with emollients applied directly to the skin or bath additives.

Antibiotics are important for treating overt secondary bacterial infections in children with atopic eczema. Flucloxacillin is useful for treating *S. aureus* infections although oral preparations are often considered unpalatable by children. Phenoxymethylpenicillin is used for *Streptococcus pyogenes*. Erythromycin is used when there is resistance to flucloxacillin or in patients with a penicillin allergy, although it is associated with nausea.[404] Side effects present less commonly with clarithromycin compared with erythromycin. Clarithromycin and erythromycin have equivalent antibacterial activity. In cases of penicillin allergy, there is a 6–10% risk of allergy to cephalosporins.

Studies investigating antimicrobial agents for atopic eczema considered reduction of skin colonisation by microbes as an outcome, as well as effectiveness in treating overt clinical infection. Reduction of *S. aureus* colonisation on the skin of children with atopic eczema using oral antibiotics (erythromycin, cloxacillin, flucloxacillin, cefuroxime axetil), topical antiseptics (chlorhexidine, potassium permanganate, an antibacterial soap (triclosan 1.5%)), acid-electrolyte water therapy and antibacterial silk clothing have been described.[405-411]

Contamination of topical treatment agents with microorganisms such as *S. aureus*, *Pseudomonas aeruginosa* and *Alternaria alternata* has been reported, although not in conjunction with cases of atopic eczema in children.[412-415]

Studies considered in this section

Six studies were identified in relation to treatment of infection associated with atopic eczema in children. Antibacterial treatment of infected atopic eczema in children was described in two RCTs,[241,416] [EL = 1–] one cohort study[417] [EL = 2–] and one case report.[418] [EL = 3] A topical steroid/antibiotic combination treatment was described in one controlled double-blind within-person

(left–right body comparison) study which combined data from children and adults.[419] [EL = 2−] Two case series reported the use of antimicrobial emollient preparations.[240,243] [EL = 3]

No studies were identified that evaluated the effectiveness of treatments for streptococcal infections, nor for antiseptics, topical antibiotics, antiseptic–topical corticosteroid combinations or antivirals as treatments for infected atopic eczema in children.

Overview of available evidence

Antimicrobial emollient preparations

A double-blind RCT compared a bath emollient containing benzalkonium chloride and triclosan with the regular bath emollient (Oilatum Plus® versus Oilatum®). All the children had atopic eczema displaying features of recurrent infection and/or frequent exacerbations (n = 30 randomised, 26 analysed). After two treatment periods of 4 weeks, some improvement in total clinical score (signs and symptoms plus area affected) were reported from baseline, although no baseline scores were reported. It was, therefore, difficult to quantify the benefit. It was also reported that there were no significant differences between groups in global change or impression scales or in self-reported severity of the condition, but no numerical data were presented. Pruritus was reported in 23% of children overall.[241] [EL = 1−]

A case series reported the use of an emollient containing antimicrobials (benzalkonium chloride and chlorhexidine hydrochloride (Dermol 500 lotion)) in children. The children were receiving treatment for eczema (whether the eczema was atopic was not reported) and in need of emollients to manage their dry skin condition. Between 81% and 87% reported that dryness and itching of the face/neck and limbs/trunk were better after 2 weeks' treatment and satisfaction rates were also high. No adverse effects were reported during the trial (n = 39).[240] [EL = 3]

A publication consisting of seven case reports of irritant reactions to a bath oil preparation containing the antimicrobials benzalkonium chloride and triclosan (Oilatum Plus) was also identified. Four of the seven were children aged up to 12 years who had infected atopic eczema. In two children who used the preparation as directed, reactions consisted of an erythematous rash that developed immediately and dry non-pruritic desquamation after 2 weeks' use. In the other two children, quantities of bath oil in excess of that recommended were used; the adverse effects were described as 'an irritant reaction' affecting the skin flexures which developed over several months, and erythema and scaling around the mouth and on the trunk (in the second case subsequent use of the same product at the correct concentration was well tolerated).[243] [EL = 3]

Antibacterials

In the other RCT, 30 children with suspected *S. aureus* superinfected atopic eczema (age range 6 months to 12 years) were randomised to either oral cefadroxil (50 mg/kg/day) in two doses or placebo for 2 weeks.[416] [EL = 1−] Twenty-eight of the 30 children had superinfections with *S. aureus* alone or in combination with group A streptococci as diagnosed by swab culture. After 2 weeks, all children on the active treatment were infection free compared with nine out of 17 in the placebo group. Severity of atopic eczema improved in both active and placebo groups, but there were no statistically significant differences between groups. Physician-rated global assessment was significantly in favour of the active treatment (P = 0.009), although patient-rated global assessment was similar in both groups.

In the cohort study, 35 children (ages 2–11 months) with atopic eczema and methicillin-resistant *S. aureus* (MRSA) infection were treated with oral nadifloxacin (15–30 g) and bufexamac ointment (a nonsteroidal anti-inflammatory; 20–40 g) or with bufexamac ointment alone for 4 weeks.[417] [EL = 2−] After 4 weeks, MRSA infections were absent in the active treatment group and continued to be so for the next 3 months, serum IgE levels were significantly reduced (P < 0.001) and severity of atopic eczema using a simple inflammation score was significantly improved (P < 0.0001). In contrast, the control group showed no resolution in MRSA infection and no changes in IgE serum levels or severity of atopic eczema.

A case report describing a 4-year-old boy with atopic eczema and an MRSA infection who developed osteomyelitis in the fingers was considered to be a rarity and not important to clinical management of eczema.[418] [EL = 3]

Topical corticosteroid and antibiotic combination treatment
In one controlled double-blind within-person (left–right body comparison) study, 81 dermatology patients, of whom 26 were children (median age 9 years, range 1–15 years), were treated with betamethasone 17-valerate 0.1% and fusidic acid 2% cream on one side of their body and betamethasone 17-valerate 0.1% alone on the other side for 1 week.[419] [EL = 2−] Sixty of the 81 patients were diagnosed as having atopic eczema (no details of severity or individual data for children were reported), and the majority of patients were judged clinically to have a degree of impetiginised dermatosis. Although all patients improved within the week of treatment, there were no significant differences in clinical improvement or reduction of bacterial colonisation between the two treatments. Patient preference tended towards the combination treatment.

7.6.3 Antimicrobial resistance

With the emergence of *S. aureus* strains with antibiotic resistance to agents such as methicillin and, more recently, fusidic acid, prolonged use of any antibiotic will sooner or later be associated with the emergence and increased prevalence of resistant strains.

It is important to distinguish between laboratory-tested antibiotic resistance of microorganisms and that of microbes on colonised or infected skin. Use of topical antibiotics results in high localised concentrations of antibiotics that can override laboratory resistance and produce a clinical response.

Studies considered in this section

Five studies were identified that evaluated antimicrobial susceptibility of infections associated with atopic eczema: three were case–control studies (one in children only and two that combined data from children and adults),[420-422] [EL = 2−] one a case series involving children only,[423] [EL = 3] and one a survey.[424] [EL = 3] Adult studies were considered because of the lack of evidence from children.

In one case–control study the bacterial flora of 50 children with atopic eczema (mean age 4.4 years) was determined on their first admission to hospital and compared with that of 20 control children.[420] [EL = 2−] Bacterial colonisation was more prevalent in the children with atopic eczema compared with control children. *Staphylococcus aureus* was the most common pathogen: 32% were phage group II (that is, strains not associated with impetigo or streptococcal scalded skin syndrome) and the density of *S. aureus* was proportional to the severity of the atopic eczema. Resistance to penicillin was present in 88% of strains and to two or more antibiotics in 38% of the strains.

Bacterial skin colonisation in another case–control study involving 33 children and adults (age range 3 months to 32 years, mean age 12.7 years) with mainly mild to moderate atopic eczema was compared with a control group.[421] [EL = 2−] There was greater colonisation with *S. aureus* in people with atopic eczema compared with controls (42% versus 5%, $P = 0.003$) and this was related to severity of the atopic eczema. All *S. aureus* isolated from people with atopic eczema were sensitive to cloxacillin, cefalexin, clindamycin and co-trimoxazole; 92% were sensitive to erythromycin, but only 13% were sensitive to penicillin and ampicillin.

One case–control study investigated 48 children and adults (age range 6 months to 75 years, mean age 6.7 years) of whom 48% had atopic eczema (no details of severity were reported).[421] [EL2−] Seventy-eight percent of *S. aureus* isolated from people with atopic eczema were resistant to fusidic acid compared with 9.6% in non-dermatology patients; 96% of people with atopic eczema who had *S. aureus* resistant to fusidic acid had used a preparation containing fusidic acid in the previous 6 months.

One case series described antimicrobial susceptibility of *S. aureus* in 115 children (mean age 2.7 years) with moderate to severe atopic eczema.[423] [EL = 3] *Staphylococcus aureus* was isolated from 87% of children. Antimicrobial susceptibility testing showed resistance to erythromycin in 18% of cases, to roxithromycin in 19%, to fusidic acid in 6% (resistant or 'intermediately susceptible'), to amoxicillin 13% and to clindamycin in 1%. All strains isolated were susceptible to oxacillin, amoxicillin/clavulanic acid, cefadroxil and cefuroxime.

A 5 year retrospective study of the characterisation and susceptibility to fusidic acid of *S. aureus* in the Carmarthen area suggested an increased incidence of fusidic acid resistance particularly

with paediatric patients with infected eczema and impetigo.[424] [EL = 3] In children aged 10 years or younger (*n* = 255, including some children with atopic eczema), fusidic acid resistance increased from 5.1% to 24.6% between 1999 and 2001. Over the same period, prescriptions of fusidic acid preparations increased in general practice, although they remained constant in hospital pharmacies.

Evidence statement for infections associated with atopic eczema in children

The majority of children with atopic eczema have skin colonised with *Staphylococcus aureus*. A high rate of self-contamination from *S. aureus* carrier sites (nose, nails, axillae, groin and ears or from colonised skin) has been reported. [EL = 3] Where children developed overt signs of clinical infection this was usually due to *S. aureus*, although streptococcus species (principally *Streptococcus pyogenes*) were sometimes involved. Mixed infections of *S. aureus* and streptococci have also been reported. [EL = 3] Other types of bacterial infection that occur in association with atopic eczema are rare and generally thought not to be any more common in children with atopic eczema than in other children. Infection with herpes simplex (eczema herpeticum), varicella (chicken pox), molluscum contagiosum, human papillomavirus, *Pityrosporum ovale*, tinea (ringworm), yeast fungi and scabies have been documented. [EL = 3] Eczema herpeticum can be life-threatening. Varicella may exacerbate atopic eczema or present as widespread varicella resembling eczema herpeticum. No evidence was found on how to treat varicella in children with atopic eczema.

The evidence for the effectiveness of antibiotic treatments for infected atopic eczema was lacking, with the few studies identified being of poor quality. [EL = 3] The available studies provided some evidence for the effectiveness of antimicrobials, but evidence for cost-effectiveness was lacking. Irritant effects due to inappropriate or long-term use of antimicrobial emollients have been reported in a number of clinical studies.

Contamination of emollient preparations with *S. aureus* and *Pseudomonas aeruginosa* has been reported. [EL = 3]

There was evidence for increasing prevalence of resistance of microorganisms to antibiotic agents (such as fusidic acid, flucloxacillin and erythromycin) using *in vitro* tests on bacteria cultured from skin swabs of children with atopic eczema. [EL = 3]

Although there were isolated case reports of extremely rare complications of infection associated with atopic eczema, the GDG considered these to have little relevance to routine clinical practice. [EL = 3]

Cost-effectiveness

No health economics issues were identified in relation to which clinically significant infections occur secondarily to atopic eczema in children, or in relation to the signs and symptoms of such infections. Assessment should take place within routine clinical consultations and requires no additional healthcare resources. Erythromycin is as effective as clarithromycin and less costly (£2.35 for a 28-tab pack of erythromycin versus £5.39 for a 14-tab pack of clarithromycin, BNFC 2007),[232] but no studies were identified that considered the cost-effectiveness of treatment for infected atopic eczema in children.

From evidence to recommendations

Colonisation of the skin with bacteria (mainly *Staphylococcus aureus*) and overt clinical infection are both associated with an increase in severity of atopic eczema, although there is a lack of agreement as to the density at which the presence of bacterial colonisation exacerbates atopic eczema.

Eczema herpeticum (due to herpes simplex virus) is under-recognised and, if not diagnosed promptly, the child's condition may deteriorate rapidly. Eczema herpeticum should, therefore, be an indication for urgent referral. Varicella may exacerbate atopic eczema and present as widespread varicella resembling eczema herpeticum or lead to secondary impetiginisation. Molluscum contagiosum can be more extensive in children with atopic eczema than in other

children because of spread from scratching, and it often seems to worsen atopic eczema locally at the site of lesions.

The GDG believes that, owing to the potential dangers of herpes simplex virus and eczema herpeticum, treatment should be started with oral aciclovir at the first suspicion of herpes simplex virus in a child with atopic eczema in order to control the infection and prevent the development of eczema herpeticum. If eczema herpeticum is suspected, oral or intravenous aciclovir can be given depending on the clinical situation.

Some oral antibiotics are unpalatable, but in many cases there is no alternative. The GDG's view was that flucloxacillin should normally be the first-line treatment for *S. aureus* and streptococcal infection because it is active against both. Erythromycin should be used when there is local resistance to flucloxacillin and in children with a penicillin allergy because it is as effective as cephalosporins and less costly. However, erythromycin is associated with nausea. Side effects present less commonly with clarithromycin compared with erythromycin. The GDG's collective experience suggested that in cases of penicillin allergy there is a 6–10% risk of allergy to cephalosporins.

It is the view of the GDG that topical antibiotics, including those combined with topical corticosteroids, should be used to treat localised overt infection only, and for no longer than two weeks.

The GDG believes that healthcare professionals should refer to local guidelines for advice on local patterns of resistance to antimicrobials and such patterns should be reviewed regularly.

Skin swabs taken for bacteriological culture are generally of limited use owing to the universal colonisation of skin with *S. aureus* in people with atopic eczema. Skin swabs can, however, be useful where there is recurrent infection, concern about antimicrobial resistance to antibiotics commonly used for *S. aureus* infection or clinical suspicion of unusual organisms.

The GDG believes that antiseptics such as triclosan and chlorhexidine can be used as an adjunct therapy for decreasing bacterial load. Some antiseptics can be irritant and very occasionally cause contact allergic dermatitis so they should only be used at appropriate dilutions and for short periods of time.

There is potential for re-infection when products in open containers contaminated with *S. aureus* and *Pseudomonas aeruginosa* are used.

Recommendations for infections associated with atopic eczema in children (including research recommendations) are presented in Section 7.11.

7.7 Stepped approach to management

Evidence relating to the definition, identification and management of flares of atopic eczema in children, management and monitoring between flares (maintenance therapy), and optimal combinations and/or sequences for using different treatments were sought for this section.

7.7.1 Identification and management of flares

Atopic eczema is usually episodic, with the episodes being called flares (factors that might precipitate flares were described in Chapter 6 and treatments for infections that might accompany flares were described in Section 7.6). There is no universally accepted definition of a flare. The question of what is a flare has been addressed in a systematic review.[425] [EL = 1+] The review identified 15 studies that provided definitions, all of which were clinical trials of interventions to treat atopic eczema in children and/or adults (some of which are considered elsewhere in this guideline). The definitions for flare or relapse used were:

- a change in severity score above a set threshold (change in SCORAD score of 50–80% or more than 15 points; increase in TIS score of at least 4 points; increase of 70% in Costa's SSS score; or increases of more than 75% in disease activity scores) – seven studies
- a composite of an IGA score of at least 4 and topical corticosteroid use for 3 days following a 7 day period free of topical corticosteroid use – three studies
- the need to use topical corticosteroids (or systemic treatment in one study) – three studies
- an IGA score of at least 3 with a score of 2 or 3 for any two signs or symptoms (erythema, itch, papulation and induration/oedema) – one study
- a scratch score of more than 2 on a five-point scale for 3 consecutive days – one study.

The ISOLATE study, which involved children and adults from eight countries including the UK, reported disease characteristics during a flare (*n* = 2002, 39% were parents of children aged 2–13 years).[96] Flare was defined as 'a sudden worsening of symptoms requiring a physician consultation or application of prescription medication.' Children aged 2–13 years experienced a mean number of 8.7 flares per year, each lasting a mean duration of 14 days, thereby spending 33% of the year experiencing a flare of atopic eczema.

Although topical corticosteroids and topical calcineurin inhibitors have been widely used for the treatment of flares, little evidence was identified regarding their use specifically for this indication. The identified data consisted of:

- two RCTs that compared fluticasone propionate 0.05% cream with either hydrocortisone 1% (*n* = 137) or hydrocortisone 17-butyrate 0.1% (*n* = 128) in children experiencing a flare of atopic eczema (one publication)[255]
- one study involving mometasone furoate 0.1% under wet wrap dressings[250]
- three RCTs evaluating the use of pimecrolimus 1% cream to prevent progression to flares[297,302–304]
- one cohort study that considered the use of silk clothing in children experiencing a flare.[426]

The RCTs comparing fluticasone propionate cream 0.05% with the two hydrocortisone preparations reported improvements in all groups but greater improvement in total eczema score and in itch and sleep disturbance with fluticasone. This study was described in detail in Section 7.2.[255] [EL = 1+]

The RCT that considered the use of wet wrap dressings with mometasone furoate 0.1% or vehicle in children with an exacerbation of atopic eczema was described in detail in Section 7.4.[250] [EL = 1−]

The three RCTs that evaluated the use of pimecrolimus at the first sign or symptom of atopic eczema in order to prevent progression to a flare (IGA score of at least 4 and topical corticosteroids used for 3 days following a 7 day period free of topical corticosteroid use) were described in Section 7.3.[297,302–304] These studies found that the proportion of children whose condition progressed to a flare was significantly lower in children who were treated with pimecrolimus compared with vehicle (both used with emollients).

A non-randomised controlled study evaluated the effects of wearing silk clothing with antibacterial properties compared with continued use of cotton clothing in children with a flare of atopic eczema (*n* = 46, age range 4 months to 10 years).[426] 'Flare' was not defined. All children applied emollients but the use of topical corticosteroids was not permitted. After a follow-up period of 1 week, SCORAD severity scores had reduced significantly from baseline in the silk clothing group (30% reduction, *P* = 0.003), but not in the control group (2% reduction, *P* = 0.886). No between-group analysis or baseline data were reported. Therefore it was not possible to determine whether groups were similar other than in the intervention being evaluated. Among children wearing silk clothes, a significant reduction in severity (SCORAD) was reported for areas covered by silk clothes compared with similar uncovered areas in the same child (reductions of 42%, *P* = 0.001 versus 16%, *P* = 0.112).[426] [EL = 2−]

7.7.2 Management and monitoring between flares

Three double-blind RCTs considered the effectiveness of topical fluticasone propionate for reducing relapse of atopic eczema, one involving children and adults[427] and two involving adults only.[428,429] The control group in each study was the vehicle base of the topical corticosteroid preparation. Emollients were also used daily.

The studies involving adults were considered because of the relative lack of data regarding maintenance therapy in children aged 0–12 years. The first RCT evaluated fluticasone propionate 0.05% cream in children and adults with moderate to severe atopic eczema (*n* = 348, 66% aged 2–17 years).[427] Atopic eczema had been stabilised by up to 4 weeks' treatment with fluticasone propionate 0.05% cream applied twice daily before randomisation to receive a reduced dose of fluticasone or vehicle (once-daily use 4 days a week for 4 weeks, followed by once-daily use twice a week for 16 weeks). Relapse was defined as an IGA score of 3 or more (scale 0–5), and a score of 2 or 3 (on a scale of 0–3) for any of three signs or symptoms (erythema, pruritus and papulation/induration/oedema). The relapse rates were 66% in the vehicle group, whereas in children using

fluticasone propionate 0.05% cream they were 27% (OR 8.1, 95% CI 4.3 to 15.2, $P < 0.001$). The median time to relapse was 5.1 weeks in the vehicle group but could not be quantified in the fluticasone group because most were controlled at the end of the follow-up period. Individual adverse effects were not reported, although it was stated that the incidence of these did not differ significantly between groups. None of the children or adults had 'evidence of skin atrophy' (not defined). Of 44 cosyntropin stimulation tests undertaken (it was not stated whether they were undertaken in children or adults), two did not reach the required post-stimulation serum cortisol level of at least 18 µg/dl (the levels were 9 µg/dl and 17 µg/dl).[427] [EL = 1+]

Two other double-blind RCTs evaluated the use of fluticasone to treat flares and to prevent subsequent relapses of atopic eczema, but in people aged 12 years and over. The first study consisted of two treatment periods: initial treatment of the flare with one of four fluticasone options, then, following stabilisation, patients either continued with a fluticasone option or received treatment with vehicle base only ($n = 376$).[428] [EL = 1+] Patients were randomised to the whole treatment sequence at the outset. A flare was defined as a score of 4 or more on TIS.

The four options used in the initial treatment of the flare were fluticasone 0.05% cream applied once daily or twice daily, and fluticasone 0.005% ointment applied once daily or twice daily. Following the stabilisation period of up to 4 weeks, treatment with fluticasone cream or ointment, or its vehicle base, was applied for up to 16 weeks. During this time, the frequency of application was reduced to twice weekly on two consecutive evenings. The risk of relapse was significantly lower in those treated with fluticasone propionate 0.05% cream or 0.005% ointment compared with vehicle (hazard ratio (HR) 5.8, 95% CI 3.1 to 10.8, $P < 0.001$ with fluticasone 0.05% cream versus vehicle; HR 1.9, 95% CI 1.2 to 3.2, $P = 0.01$ with fluticasone 0.005% ointment versus vehicle). Median time to relapse was longer than 16 weeks (the duration of the study) with both fluticasone preparations, compared with 6.1 weeks in both vehicle groups. Adverse events noted during the stabilisation phase were three reports of visual signs of skin atrophy (two having telangiectasia and striae and one having telangiectasia).[428]

The second study involving adults also reported a lower relapse rate in those treated on two consecutive days per week with fluticasone propionate 0.005% ointment compared with vehicle for 16 weeks ($n = 54$).[429] However, it was not possible to tell from the data reported whether groups were similar at baseline in parameters other than the intervention. [EL = 1−]

7.7.3 Combining treatments

When considering how to combine treatments for atopic eczema in children the GDG aimed to evaluate:

- the effectiveness and cost-effectiveness of combination products (for example, a topical corticosteroid with an antimicrobial versus either alone) – see Section 7.6
- the effectiveness and cost-effectiveness of treatments used in combination (for example, topical corticosteroids alongside emollients) versus one of the treatments used alone
- the effectiveness and cost-effectiveness of different treatment strategies (for example, short-term use of a potent topical corticosteroid versus longer term use of a less potent preparation, or topical corticosteroids compared with topical calcineurin inhibitors for the management of flares)
- how to sequence treatments for optimal effect (that is, the effective and cost-effective use of available treatments) including which treatments to use in specific circumstances (considering severity, signs and symptoms, health-related quality of life and other criteria affecting quality of life).

There was a lack of evidence for how to combine or sequence treatments for atopic eczema. There were few trials of true treatment alternatives (for example, topical corticosteroids compared with topical calcineurin inhibitors), and thus it was not possible to establish an optimal sequence of treatments in terms of clinical effectiveness data alone.

An RCT that considered different strategies for using topical corticosteroids was described in Section 7.2.[254]

Some of the trials of antihistamines reported that they were used in conjunction with a topical corticosteroid and emollient, but the comparison in these trials was only placebo.[339,342] [EL = 2+]

Similarly, in studies evaluating topical calcineurin inhibitors, emollients were used in all treatment arms. The reporting of whether emollients were also used in studies involving topical corticosteroids was generally poor.

Evidence statement for stepped approach to management

In clinical trials, a flare has been defined in a variety of ways, predominantly involving severity or IGA. A minority of studies defined a flare in terms of the need to use certain additional treatments, which does not inform when to use these treatments. There was no published consensus on how to define or identify a flare.

There were some data showing that topical corticosteroids are effective when used specifically to treat a flare. [EL = 1+] RCTs showed that pimecrolimus 1% cream reduced the progression to flare compared with vehicle when used at the first sign or symptom of atopic eczema. [EL = 1+] No conclusions could be drawn from one small study of poor quality that considered the use of silk versus cotton clothing for 1 week in children who experienced a flare of atopic eczema. [EL = 2−] When used following the stabilisation of a flare, maintenance treatment with fluticasone propionate (0.05% cream or 0.005% ointment) applied twice weekly for 16–20 weeks was more effective than its vehicle base in reducing the relapse rate in children. [EL = 1+]

No evidence to evaluate the optimal combination or sequence of treatments for atopic eczema in children was identified.

Cost-effectiveness

There was a lack of evidence of the effectiveness of combinations of treatment and consequently there was no evidence of the cost-effectiveness of these treatments. Economic evaluation requires treatment outcomes to be evaluated using the same units to allow direct comparison of the costs and health benefits of treatment alternatives. These data were not available and therefore it was not possible for the GDG to reach any meaningful consensus as to the likely comparative advantage of one combination of treatments over another.

From evidence to recommendations

In the absence of consistent definitions for what constitutes a flare, the GDG's view was that in clinical practice a flare should be defined as an increase in clinical severity (redness, oedema (swelling) or itching) of the condition. Parents usually recognise when a child's atopic eczema is flaring because it becomes more itchy and red and the child scratches more, thus the child will be complaining or showing that their skin is causing a problem over and above what they would normally expect.

The GDG believes that it is important to try to identify what is precipitating a flare because this will influence the treatment choice or intervention. Additionally, it is important to recognise a flare early because early treatment prevents damage to the skin barrier which results from the itch–scratch cycle. In the GDG's view, treating dry skin, which can be an early sign of a flare, with an emollient may prevent worsening of a flare.

The data regarding prevention of flares in adults are probably only relevant to older children with chronic established atopic eczema which is constant; the data may not be transferable to younger children with complete clearance between flares and who might thus be using the topical corticosteroid unnecessarily.

In the absence of published evidence regarding optimal strategies for combining or sequencing treatments for atopic eczema in children, the GDG's consensus was that treatment should follow a stepped approach, taking into account the severity of and degree of control of the atopic eczema, possible trigger factors and the effect on quality of life and psychosocial wellbeing of the child and their family/caregivers. Emollients should always be used as minimal maintenance therapy, and their use should be continued during flares. One or more of the following treatments should be used in addition to emollients during flares: topical corticosteroids, topical calcineurin inhibitors, dry bandages or medicated dressings (including wet wraps), antihistamines, appropriate treatment for infected eczema, and, in some severe cases, phototherapy and systemic treatments

(see Section 7.8). For mild atopic eczema, treatment options are emollients and mild topical corticosteroids; for moderate eczema (excluding the face and neck), emollients can be used with moderate topical corticosteroids, tacrolimus or bandages; for severe eczema (excluding the face and neck), treatments include emollients, potent topical corticosteroids, tacrolimus, bandages, phototherapy and systemic treatments. Treatment should be stepped up or down according to severity and clinical response.

Recommendations for stepped approach to management (including research recommendations) are presented in Section 7.11.

7.8 Phototherapy and systemic treatments

This section covers phototherapy and treatments given orally or by injection that modulate the immune response.

Studies considered in this section

The HTA of treatments for atopic eczema was checked for evidence regarding phototherapy or systemic immunomodulators in children with atopic eczema.[26] Where available, RCTs evaluating the effectiveness of these interventions in children with atopic eczema were considered in this section. Where RCTs were not available, studies of any design were considered.

7.8.1 Phototherapy

Phototherapy involves exposure to ultraviolet light (UVA or UVB rays) under controlled conditions. Psoralen, a photoactive drug, can be given with UVA (known as PUVA) to enhance the effectiveness of phototherapy. The mechanism of action of phototherapy in atopic eczema is not completely understood but is believed to involve immunosuppression.[26] The wavelength of UVB phototherapy is 290–320 nm, narrow-band UVB 311–313 nm, and UVA 320–400 nm. The risks of developing skin cancers following long-term damage to the skin by ultraviolet light are well known and these relate to high lifetime cumulative dosages. The risk associated with one course of phototherapy is thought to be extremely low to negligible.[430]

Overview of available evidence

Studies reporting the use of phototherapy using UVB (including narrow-band), UVA, and PUVA in the treatment of atopic eczema in children were identified.

Narrow-band UVB
The use of pimecrolimus 1% cream in combination with narrow-band UVB irradiation was evaluated in a 6 week RCT in children and young people (n = 26, aged 5–17 years).[431] [EL = 1−] No other treatments (including emollients) were allowed during the study. The two treatment arms were as follows: pimecrolimus applied to the whole body and irradiation to one half; and pimecrolimus applied to half the body and irradiation to the whole body. Within-patient comparisons were reported for each treatment arm, which found no significant difference in improvements in EASI scores (score reductions of 53–59%). Changes in pruritus scores were also similar in all patients. Two patients reported intractable generalised pruritus and tender erythema.[431] [EL = 1−]

A cohort study aimed to compare the effects of narrow-band UVB irradiation on the skin flora of children with atopic eczema and vitiligo (n = 20, mean age 9.5 years).[432] [EL = 2−] The amount of UVB exposure was the same in both groups although no details of the regimen or duration of follow-up were reported. Levels of cutaneous aerobes, anaerobes, staphylococci (including *Staphylococcus aureus*) fell; the changes were reported to be statistically significant ($P < 0.05$), but it was not clear whether this was from baseline or between groups (or both). SCORAD scores fell significantly from baseline in children with atopic eczema. Adverse effects of treatment were not considered.[432] [EL = 2−]

Three case series described the use of various phototherapy regimens in children with a range of skin conditions and reported data for children with atopic eczema separately.[433-435]

The first case series described the use of UVB given three times a week for 7–20 weeks, mean 15 weeks (*n* = 20, aged 16 months to 11 years, 25% with atopic eczema).[433] The number of treatments given ranged from 20–61 (mean 41). Outcomes were reported vaguely, with all children 'moderately improved' (not defined). Burning and erythema necessitating the temporary discontinuation of treatment was reported in two children.[433]

The second case series reported the outcomes of combined UVA and UVB treatment, given three or five times per week for an unknown duration (*n* = 53, aged 4–16 years, 40% with atopic eczema).[434] Reduction in SCORAD score of at least 90% was reported in 45%, reduction of 70–90% in 23%, and reduction of 50–70% in 32%. Four people experienced mild erythema.[434] [EL = 3]

The third case series described the outcomes of narrow-band UVB phototherapy (*n* = 77, aged 4–16 years, 32% with atopic eczema).[435] Details of the treatment regimen (frequency of phototherapy and its duration) were lacking, as were demographic details. Of the children with atopic eczema, 68% had minimal residual disease at the end of treatment. Adverse effects (total group) included erythema (30%), anxiety (6.5%), and infection with herpes simplex (2.6%) or varicella zoster (1.3%).[435] [EL = 3]

The use of narrow-band UVB in children and young people with atopic eczema was also described in a letter (*n* = 40, aged 2.5–15 years).[436] Details of the frequency of phototherapy and duration of treatment were again lacking. It was reported that 23% had an excellent response (not defined), 58% a good response, and 20% a poor response (treatment discontinued). Longer term follow-up data for 24 of the 32 patients who completed treatment were reported, which showed relapse rates of 20% within 6 weeks, 50% at 3–4 months, and 25% at 6–9 months; the remaining patient was in remission at 2 years. Adverse effects reported were facial erythema in 35%, xerosis in 25%, herpes labialis in 5% and burning in 2.5%.

One case series[437] described all paediatric patients with severe atopic eczema who had undergone narrow-band UVB phototherapy between 1999 and 2005 in a particular clinic (*n* = 60, aged 4–16 years). Adverse events were experienced by 14 children. These included well-demarcated erythema, painful erythema and reactivation of herpes simplex virus. Follow-up data were incomplete and there was no comparator group. [EL = 3]

PUVA

Two case series described the response to PUVA therapy. In the first, PUVA was given twice or three times a week in children with severe atopic eczema (*n* = 53, aged 6–16 years).[438] After a mean of 9 weeks' treatment, 74% achieved at least 90% clearance of their eczema. The remainder did not have clearance or 'near' clearance; most withdrew from treatment. Overall, 38% also received oral prednisolone during the early phase of treatment, which was then gradually tapered off. The cumulative dose of UVA and the number of irradiation treatments in children also receiving prednisolone was lower. At 1 year, 69% remained in remission. Adverse effects reported were the development of freckles (30%), blistering (19%), recurrent herpes simplex (9%) and acute exacerbations of asthma (4%). It was reported that there was no evidence of corneal or lens opacities, and that liver function tests remained normal.

In the second case series, children and young people (aged 10–14 years) were treated with PUVA, for an unknown duration (*n* = 15).[439] Clearance or near clearance was achieved in all except one person who withdrew from the study because of intolerance to the heat of the irradiation cabinet. Short courses of oral prednisolone were also taken by one-third of patients when it was not possible to increase the dose of UVA irradiation owing to skin irritability. Time to remission ranged from 0.3 to 1.8 years (median 1 year), and duration of remission from 0.25 to 4.2 years (median 1.1 year). Adverse effects reported were freckles (20%) and cutaneous herpes simplex and photo-onycholysis (7% each).[439] [EL = 3]

Cost-effectiveness

No evidence was identified regarding the cost-effectiveness of systemic immunomodulators or phototherapy for the treatment of atopic eczema in children.

7.8.2 Systemic treatments

Overview of available evidence

Studies reporting effectiveness data for ciclosporin, azathioprine, systemic corticosteroids, interferon gamma and intravenous immunoglobulin in the treatment of atopic eczema in children were identified. It should be noted that interferon gamma is not available as a treatment for atopic eczema in the UK. Most available data related to ciclosporin. There were limited numbers of RCTs, with most data being reported as small case series or case reports for all the treatments considered. No studies evaluating the use of methotrexate, mycophenolate mofetil or systemic tacrolimus in children with atopic eczema were identified.

Ciclosporin

The studies identified for ciclosporin in children with atopic eczema consisted of one RCT,[440] four case series,[64,441-445] and four publications describing one or more cases.[446-449] Only children with atopic eczema who had failed to respond to other treatments were included in these studies.

The RCT of ciclosporin use in children compared two treatment strategies – a 3 month course and 12 months' continuous use, both at a dose of 5 mg/kg/day (*n* = 43 randomised, 40 analysed, age range 2–16 years).[440] [EL = 1−] No significant differences were reported between groups in any outcome (severity (SASSAD), or body surface area affected) at 1 year. More than half (57%) of those in the 3 month group were treated continuously or had extended treatment periods. Quality of life was also assessed, but the method used and results obtained were not reported. Adverse effects occurring in at least 5% of each treatment group were nausea, paraesthesia, hypertrichosis, swollen gums, headache, rhinitis, upper respiratory tract infection, abdominal pain, folliculitis and hyperuricaemia.[440]

In the first case series, the response (not defined) to ciclosporin therapy was 'good' or 'excellent' in 89% (median duration 6 weeks; *n* = 18, aged 3–16 years). The initial dose used was 5–6 mg/kg, thereafter the dose was titrated according to response. The relapse interval (relapse defined as the requirement for potent topical corticosteroids or further systemic treatment) was a median of 6 weeks (range 0–38 weeks). One child experienced nausea, but otherwise there were no adverse effects. There were no significant changes in serum creatinine or in blood pressure.[441] [EL = 3]

In a case series of children treated with ciclosporin 5 mg/kg for 6 weeks, significant improvements were reported in all outcomes (severity (SASSAD), extent, pruritus, sleep disturbance, irritability, reduction in topical corticosteroid use; *n* = 27, aged 2–16 years). However, results were reported only in graphs with no numerical changes reported. Significant improvements in quality of life were also reported, although the measurement tool used was not specified. In terms of global response and tolerability, more than 75% reported at least considerable improvement in symptoms, and at least 92% reported good or very good tolerability (the child's/parent's and investigator's assessments gave similar results). The most common adverse effects were headaches (26%), abdominal pain (22%) and nausea (15%). There were no statistically or clinically significant changes in serum creatinine levels or in blood pressure. There was one case of a transient increase in serum bilirubin levels which normalised (treatment was not discontinued).[64] [EL = 3]

In another case series, children with severe atopic eczema were treated with ciclosporin 2.5 mg/kg/day which could be increased to 5 mg/kg/day (*n* = 10, aged 22–189 months).[442-444] After 8 weeks' treatment SCORAD scores had reduced by 35% or more in nine children (the reduction was 32% in the remaining child). Seven of the nine children's atopic eczema did not relapse during the additional 4 week follow-up period. There were no cases of hypertension and no significant changes in serum creatinine levels. Serum bilirubin levels increased by 2.5 µmol/l, the increase being statistically significant. Tolerability was regarded as good or excellent in nine children by their own or their parents' assessment and in eight children by the investigator's assessment.[442] The quality of life of the mothers of these children was also assessed. Of the five subscales of the German FEN quality of life assessment tool, there were significant improvements in the psychosomatic wellbeing and the emotional coping of the children's mothers.[443] [EL = 3]

In the fourth case series, children aged 2–16 years with severe atopic eczema were treated with ciclosporin 2.5–5 mg/kg/day for 8 weeks. The SCORAD score fell significantly from baseline ($P < 0.001$). Greater effectiveness was reported in children only colonised with *S. aureus*

compared with those clinically infected with *S. aureus* (mean SCORAD scores were lower, $P < 0.01$). Other data were only reported in graphs. A significant reduction in *S. aureus* density was seen in colonised but not infected children.[445] [EL = 3]

Other identified information regarding the use of ciclosporin consisted of case reports containing varying amounts of detail (not providing case history, or only noting dosages used, or reporting specific adverse effects).

One publication described three children aged 2, 4 and 5 years who had been treated successfully with ciclosporin 5 mg/kg/day for 8 weeks without any adverse effects. Relapse occurred once treatment stopped, but after varying intervals.[446]

Another case report described a change in formulation of ciclosporin in a child aged 2.5 years. Treatment was switched from one formulation (Sandimmun®; oral form no longer available in the UK) after 6 weeks of therapy to another formulation (a microemulsion, Neoral®, currently the only oral formulation of ciclosporin available in the UK). Treatment was changed because of deterioration in the child's atopic eczema. After 8 weeks' treatment with the microemulsion, the investigator-rated severity score reduced by 55%, and itching, sleep and irritability all improved by 37–47% (rated by mother).[447] [EL = 3]

In one case report, reduction in raised blood pressure was seen during treatment with ciclosporin 5 mg/kg/day in a 6-year-old boy with severe atopic eczema, asthma and hay fever. The raised blood pressure at baseline was believed to be due to stress related to atopic eczema, sleep deprivation or previous/concurrent treatment, which included potent topical corticosteroids, inhaled corticosteroids and 'occasional' oral prednisolone. Thus the normalisation of blood pressure was considered to be due to successful management of the condition with ciclosporin.[448] [EL = 3]

One publication reported two cases of raised alkaline phosphatase levels in children aged 2 years who were treated with ciclosporin. The levels normalised after treatment withdrawal.[449] [EL = 3]

Systemic corticosteroids

A crossover double-blind RCT compared 4 weeks' treatment with oral plus nasal beclometasone dipropionate with placebo in children (n = 27, aged 3–14 years) with atopic eczema.[450] The oral beclometasone used was the contents of capsules for inhalation mixed with some water; the inhaled product was a proprietary nasal spray. Significantly greater improvements in redness, surface damage and lichenification were seen with beclometasone compared with placebo. The daytime itch score and use of antihistamines were significantly lower in the systemic corticosteroid group, while sleep loss scores and daily use of topical corticosteroids were not significantly different between groups. Parental global assessment indicated that children fell into the 'no change' to 'somewhat better' category, but the difference between groups was statistically significant, the children treated with beclometasone tending towards 'somewhat better'. No adverse effects were reported during treatment.[450] [EL = 1−]

Other isolated reports of the use of systemic corticosteroids for atopic eczema in children were identified, but only vague details were provided in the reports. A small case series reported the effectiveness of a 3 day course of intravenous methylprednisolone 20 mg/kg/day in children with severe atopic eczema and raised serum IgE levels in whom conventional treatment had failed (n = 7, aged 3–14 years). Improvements in severity were reported in five of the children (reduction in a generic score from a mean of 49 to less than 8), which persisted for a mean of 10 months (range 3–18 months). The other two children only experienced mild and transient improvement. IgE levels were 'unaffected' by therapy (no further details reported). Adverse effects were not considered.[451] [EL = 3]

The successful use of oral prednisone (5 mg daily) in a 7-year-old child with atopic eczema in whom standard treatment (including topical corticosteroids and emollients) had failed was documented.[452] [EL = 3]

Another publication reported the worsening of atopic eczema in two children (aged 6 and 8 years) on withdrawal of a systemic corticosteroid (the drug was not specified).[453] [EL = 3]

Azathioprine

One case series described the use of azathioprine 2.0–3.5 mg/kg/day to treat severe atopic eczema in children who had normal thiopurine methyltransferase levels (n = 48, aged 3–16 years).[454] 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 were not quoted. (Thiopurine methyltransferase is an enzyme that metabolises azathioprine, and it is believed that those with low levels are at higher risk of developing myelosuppression from the drug). Based on parental global assessment of the child's condition at 3 months, 58% had an excellent response (at least 90% improvement) and 27% had a good response (60–90% improvement), while the remaining 15% were classified as having an inadequate response (less than 60%). Overall, 48% were also treated with prednisolone at some time during azathioprine treatment. Adverse effects during treatment were one case each of eczema herpeticum, gastrointestinal symptoms (nausea, vomiting, diarrhoea) and a possible hypersensitivity reaction (manifested as urticaria and vomiting). There were no cases of neutropenia. Other transient effects were abnormalities of liver function tests (10%), lymphopenia (31%), and thrombocytopenia (2%).[454] [EL = 3]

In another publication, the same investigators described azathioprine treatment in two children (aged 7 and 14 years) who had low thiopurine methyltransferase levels (below the normal range). The 14-year-old was treated with 1.25 mg/kg/day for 10 months. The 7-year-old was treated with 1 mg/kg/day for 8 months. Improvement in the atopic eczema was seen after 2 weeks' azathioprine treatment (more than 90% in one, and 'almost clear' in the other). The 7-year-old had a varicella zoster infection during treatment which was treated successfully. Benefit was reported to be sustained for 8–10 months (no further details were given for beyond this period) and oral corticosteroid therapy was withdrawn in both cases.[455] [EL = 3]

Methotrexate

No studies evaluating the use of methotrexate to treat atopic eczema in children were identified. Two case series in adults with moderate to severe atopic eczema reported improvements in the majority of patients treated for a median or fixed duration of 3 months (total *n* = 32).[456,457] Methotrexate was given by intramuscular injection or orally in one study[456] and orally in the other.[457] In both studies, treatment was given or taken once weekly. Adverse effects reported included nausea and transient increases in liver enzymes.

Interferon gamma

One placebo-controlled double-blind RCT,[458] an associated long-term follow-up study[459] and five case series or case reports[460–464] described the use of interferon gamma to treat atopic eczema.

The RCT included children and adults (age range 3–65 years), with some data reported separately for those aged 3–20 years (*n* = 83, 25% aged 3–20 years).[458] [EL = 1+] However, the relative proportion of people aged 3–20 years differed between groups, with six treated with interferon gamma and 15 treated with placebo.

Interferon gamma 50 μg/m^2/day by subcutaneous injection was self-administered by patients (or carers in the case of children, presumably) for 12 weeks. At the end of treatment, the proportions reporting at least 50% improvement were significantly higher in the interferon gamma than the placebo group (45% versus 21%, *P* = 0.016 based on the investigator's assessment, and 53% versus 21%, *P* = 0.002 based on the patient's or carer's assessment). In those aged 3–20 years, the patient/carer ratings were 67% versus 20% (investigator's assessment was not reported). Of six signs or symptoms evaluated, significantly greater improvement was reported with interferon gamma than placebo for erythema and excoriations, but there were no significant differences between groups for the other four parameters (pruritus, induration, dryness and lichenification). The quantity of topical corticosteroid used (triamcinolone acetonide 0.1%) was not significantly different between groups. Adverse effects reported were headaches (60% interferon gamma versus 28% placebo, *P* = 0.004), myalgia and chills (30% interferon gamma, not reported for placebo), transient granulocytopenia (12.5% versus 2.5%), and mild transient increases in liver transaminase levels (16.3% versus 2%).[458]

Twenty-four patients (aged 11–57 years) from the RCT were treated with interferon gamma for 1 year, and 16 patients for 2 years.[459] [EL = 3] Reasons for discontinuation between years 1 and 2 were inconvenience and non-adherence (two each), and improvement without therapy, ineffectiveness, flu-like symptoms and unknown reasons (one each). Significant improvements in most outcomes were reported at both year 1 and year 2 (total body surface area affected, global assessment, total clinical severity and individual parameters (erythema, excoriations, pruritus, induration, dryness and lichenification)). Improvements in the associated atopic symptoms allergic

conjunctivitis and rhinitis were also significant, but not asthma. No significant changes in serum IgE levels were reported. Increases in the liver enzymes aspartate aminotransferase and alanine aminotransferase were evident at year 1 and fell towards baseline at year 2. Serum creatinine was mildly elevated at year 2 but remained within the normal range. Adverse effects reported were 'transaminitis' (16%), headache, malaise, acne vulgaris, neutropenia, arthralgia (8% each), fever/chills, gastric and oesophageal ulcers, splenomegaly, herpes zoster, molluscum contagiosum, respiratory 'congestion', theophylline toxicity and postherpetic neuralgia (4% (*n* = 1) each).[459]

A second case series including children and adults (aged 3.6–57 years) reported the effects of interferon gamma therapy for atopic eczema (*n* = 15, 60% aged under 16 years).[460] [EL = 3] Treatment with interferon gamma was for a minimum of 22 months (range 22–76 months, median 36 months), at a dose of 50 μg/m^2 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. The results showed a reduction in both total body surface area affected and in total severity score over time. Growth charts used to monitor patients aged under 16 years did not appear to show any effects on growth during the study. Treatment-related adverse effects were headaches (47%), fever (13%) and chills (6.7% (*n* = 1)).[460]

The third case series aimed to evaluate immunological parameters as predictors of success of interferon gamma therapy in patients with severe atopic eczema that had not responded to topical corticosteroids and antihistamines (*n* = 68, age range not reported).[461] The dose used was 2 × 106 IU/m^2 for 5 days in the first week, three times a week for 3 weeks, and then twice a week for another 2 weeks. Some severity data were also reported, with more than 20% (mean 63%) reduction in severity in 34%, less than 20% (mean 8%) in 44%, and no response in the remainder (22%). Adverse effects were not considered.[461]

The other three publications documented the use of interferon gamma in a total of ten children.[462-464] The first publication reported that treatment in a 2-year-old boy was unsuccessful and was changed to interferon alpha, after which clearance of atopic eczema lesions was seen following 6 months' treatment. The severity of the condition reduced in a 5-year-old treated with interferon gamma three times a week for 20 weeks.[462]

The second publication documented a lack of response in a 4-year-old boy and a 5-year-old girl. Both children had previously been treated unsuccessfully with topical corticosteroids.[463]

The third publication discussed the histories of children in whom the authors used interferon gamma as a last resort, all initially treated as hospital inpatients.[464] The children had severe atopic eczema and other conditions or problems. However, the outcome of interferon treatment was not described clearly: it seemed that in two children treatment was successful, in one it was not, and no information was given regarding the outcomes of the other three.[464] [EL = 3]

Intravenous immunoglobulin

One narrative review described literature identified in relation to the use of intravenous (IV) immunoglobulin in children with atopic eczema, which consisted of three publications.[465] In four children, IV immunoglobulin was used to treat Kawasaki syndrome or idiopathic thrombocytopenia purpura, in which improvement ('remission') of their coexisting atopic eczema was noted within 7 days. A case report of an 8-month-old boy treated for thrombocytopenia did not find improvement of his atopic eczema. The third publication reported improvement in 'skin score' and in levels of cytokines (including interleukin and interferon levels) in five children with atopic eczema who were treated with IV immunoglobulin.[465] [EL = 3]

Mycobacterium vaccae

One double-blind RCT evaluated the effects of killed *Mycobacterium vaccae* on atopic eczema in children with moderate to severe disease (*n* = 166, 93% completed and analysed, aged 5–16 years).[63] [EL = 1−] At 12 or 24 weeks following a single intradermal injection of the preparation (either 1 mg or 0.1 mg, or placebo), there were no significant differences between groups in any outcome (severity (SASSAD), body surface area affected, patient's global assessment, pruritus, sleep, topical corticosteroid use, or quality of life (CDLQI)). Overall, 19% had injection-site reactions (induration and erythema), and 13% had atopic eczema that was believed to be due to the injection given (32% reported atopic eczema as an adverse effect overall).

Evidence statement for phototherapy and systemic treatments

One RCT of poor quality reported no significant difference between 6 weeks' treatment with pimecrolimus 1% cream alone or pimecrolimus 1% cream in combination with narrow-band UVB. [EL = 1−] Case series describing other phototherapy regimens in children with atopic eczema were also identified (UVB, UVA plus UVB, narrow-band UVB and PUVA), but reporting of the actual regimens used and of outcomes was generally poor. Some benefit, variously defined, was noted for a proportion of patients. Adverse effects reported include erythema, burning, blistering, dryness and the development of freckles. [EL = 3]

There was some evidence for the effectiveness of ciclosporin, systemic corticosteroids, azathioprine, interferon gamma and intravenous immunoglobulin for the treatment of atopic eczema in children, but no evidence of its cost-effectiveness. No evidence evaluating the clinical or cost-effectiveness of methotrexate or of mycophenolate in children was identified.

One RCT found no significant difference between a 3 month and a 12 month course of ciclosporin therapy in children in terms of severity or body surface area affected. [EL = 1−] Case series reported a response in the majority of those treated with ciclosporin, although the outcomes measured and the level of detail given for outcomes were lacking. Adverse effects reported included headaches, nausea and abdominal pain. None of the studies reported significant changes in blood pressure or in serum creatinine levels. [EL = 3]

A short-term crossover study of beclometasone given orally and by inhalation reported greater improvements in itch, redness, surface damage and lichenification compared with placebo, but no significant difference for sleep loss or daily topical corticosteroid use. Global assessment indicated only small benefit. [EL = 1−] Other isolated reports of systemic corticosteroid use mainly reported some response, although there were also reports of unsuccessful treatment outcomes and withdrawal effects. [EL = 3]

Case series of azathioprine use (48% of whom were also treated with systemic prednisolone at some time during treatment) reported response in the majority at 3 months. [EL = 3]

One double-blind RCT in children and adults found that significantly more patients treated with interferon gamma than placebo had a 50% or greater response at 3 months. Two of six signs/symptoms were significantly improved, with no significant difference between the groups in changes in the other four. Longer term use (up to 2 years) in some of the patients treated (aged 11 years and above) indicate sustained benefit. Other case series indicated improvements in severity and in total body surface area affected, while case reports noted both success and failure of interferon gamma treatment.

Some reports of response to IV immunoglobulin were identified in the literature, when used to treat atopic eczema, or indirectly when the intervention was used to treat another condition.

No evidence regarding the cost-effectiveness of systemic treatments or phototherapy for the treatment of atopic eczema in children was identified.

From evidence to recommendations

Phototherapy and systemic treatments have only limited evidence of effectiveness for some children with severe atopic eczema and have potentially serious adverse effects. The GDG believes that phototherapy should be considered before systemic treatments unless there are contraindications such as very fair skin or family history of skin malignancies. Phototherapy and systemic treatments should only be offered under close supervision by specialists experienced and trained in their use as they require close monitoring for safety aspects. After weighing up the benefit and harm of treatment and the costs (drug and equipment costs and specialist time), the GDG took the view that phototherapy and systemic treatments should be used only in severe cases of atopic eczema in children where other management options have failed or are not appropriate, and where the atopic eczema has a significant impact on quality of life. It is the GDG's view that assessment and documentation of severity and quality of life should always be undertaken prior to initiating treatment with systemic treatments or phototherapy.

Recommendations for phototherapy and systemic treatments (including research recommendations) are presented in Section 7.11.

7.9 Complementary therapies

Complementary therapies are defined as a group of therapeutic and diagnostic disciplines that exist largely outside the institutions where conventional healthcare is taught and provided. These therapies can be used alongside conventional care, as the term 'complementary therapies' implies. Patients may also choose to use complementary therapies instead of mainstream medicine (that is, as 'alternative therapies'). Complementary therapies have become more widely used over the past two decades, but many practitioners/practices in the UK are largely unregulated. In 2000, a report on complementary and alternative therapies by the House of Lords Select Committee on Science and Technology recommended that 'in order to protect the public, professions with more than one regulatory body should make a concerted effort to bring their various bodies together and to develop a clear professional structure.' In 2005, the Department of Health published a consultation document regarding the statutory regulation of herbal medicine and acupuncture and the Department is in the process of setting up a stakeholder working group to move towards regulation of these two professions.

Until recently, the majority of over-the-counter herbal medicines were classified and sold as food supplements, with little control over their quality and contents. New EU regulations regarding the regulation of herbal medicinal products came into force in the UK on 31 October 2005 to address this situation.[466] Section 12(1) of the Medicines Act 1968 that allows herbal practitioners to make up personal prescriptions is also being considered for reform regarding the preparation of herbal mixtures by a third party. It is proposed that any third party producing herbal products must be able to prove good manufacturing practice.

The use of complementary therapies in children with atopic eczema and their parents/guardians was surveyed in a secondary care setting in Leicester.[467] [EL = 3] The mean age of the children was 7.3 years (range 0.6–17.1 years) and ethnic origin was 59% white, 35% Indian, 3% Afro-Caribbean and 3% mixed race. Forty-six of the 100 children/parents questioned had used, or were currently using, complementary therapies. Of the 54 who had not yet used complementary therapies, 31% said they intended to try this in the future. The most commonly used therapies were Chinese herbal medicine (43%), herbal medicine (41%) and homeopathy (35%). Of the 74 episodes of treatment experienced by the users, in 26 of the incidents the child/parent felt that their atopic eczema had improved, while 39 reported that there was no change; in the remaining nine incidents the child/parent reported the eczema had deteriorated. There was a strong association between the use of complementary therapies and ethnicity. Fifty-four percent of users did so because their conventional treatment was not working, with 17% saying they were worried about side effects of conventional treatment. Thirty-nine percent of all children/parents felt that complementary therapies were safer than conventional medication although only 14% thought they were more effective. Fifty-one percent were happy to combine both types of treatment.

In another UK survey involving 80 children with atopic eczema (mean age 3.9 years), 34 (43%) had used at least one form of complementary medicine for their condition, of which herbal medicine (41%) and homeopathy (24%) were the most popular. Of these children, 44% expressed some improvement (most commonly reduction in itch), while 10% experienced deterioration in their atopic eczema.[468] [EL = 3]

Studies considered in this section

The HTA of treatments for atopic eczema was checked for evidence relating to complementary therapies.[26] Where available, RCTs evaluating the effectiveness of complementary therapies in children with atopic eczema were considered for this section. Where RCTs were not available, or were too short in duration to consider adverse effects, observational studies of any design were considered.

Overview of available evidence

Studies evaluating the following complementary therapies in children with atopic eczema were identified:

- homeopathy
- Chinese herbal medicine

- massage
- hypnotherapy
- aromatherapy
- a honey, beeswax and olive oil mixture
- *Nigella sativa* (black seed) oil
- gamma linolenic acid (an essential fatty acid).

No studies evaluating the effectiveness or safety of acupuncture, acupressure, meditation, relaxation techniques, naturopathy, hydrotherapy, balneology or Western herbal medicines were identified.

Homeopathy

No controlled trials evaluating the use of homeopathy in childhood atopic eczema were identified. One observational study followed children (mean age 6.7 ± 4.1 years) for a total of 24 months following an initial homeopathic consultation and course of treatment for a variety of diagnoses (n = 1130, 20% of whom had atopic eczema).[469] [EL = 3] The main outcomes were child's/parent's and physician's assessments (rated on a scale from 0 to 10), and quality of life at 0, 3, 12 and 24 months. All parameters improved compared with baseline at 24 months according to the child's/parent's and practitioner's assessments (quality of life was assessed by parents for children under 6 years, $P < 0.001$). No individual data for atopic eczema were reported.

One case series reported the use of homeopathy in children and adults with predominantly mild to moderate atopic eczema (n = 36, 25% of whom were aged 11 months to 12 years).[470] [EL = 3] The children received individualised homeopathic treatment between June 1995 and June 2001 in an Indian homeopathic medical college. Results were reported separately for children with skin symptoms only (n = 6), and for those with skin and respiratory symptoms (n = 3). Results were presented in terms of percentage relief/improvement. In the skin symptom only group, 3/6 were rated 99% with no new exacerbations, 2/6 were rated 60% with occasional exacerbations, and 1/6 was rated 20% (negative result) and discontinued treatment. In the skin and respiratory symptom group, 2/3 were rated 99%, 90% with no new exacerbations and 1/3 was rated 40% with new recurrence.

No safety data were identified in relation to homeopathy in children with atopic eczema.

Herbal medicine

One RCT considered the effectiveness of Chinese herbal medicine in children with atopic eczema, and a 1 year follow-up study of the same children provided longer term data.[471,472] [EL = 1− and EL = 3, respectively] The RCT included 37 children with non-exudative atopic eczema with an age range of 1.5–18 years. The main outcome measures were mean severity score (0–3), erythema, surface damage and adverse events (including creatinine and endogenous steroid excretion). Median percentage changes from baseline of the clinical scores for erythema were 51% for Chinese herbs compared with 6.1% for placebo. The corresponding figures for surface damage were 63.1% and 6.2%. No safety issues were reported. The 1 year follow-up study of the children (all on active treatment) concluded that Chinese herbal medicine in the medium term proved helpful for approximately half the children who took part in the original study. However, since these studies were published, a Cochrane review has reported that the product used in the studies has ceased to be manufactured.[473]

A case series investigated a pentaherbs capsule treatment for atopic eczema in Chinese children (n = 9, aged 5–13.5 years).[474] [EL = 3] Treatment with three pentatherb capsules was given twice daily for 4 months. After 3 months, 7/9 children had a significant reduction in their SCORAD severity score (from 60.3 to 40.0, P = 0.008). Significant differences were also noted in the extent, intensity, pruritus and sleep loss components of the SCORAD scale ($P < 0.05$ for all). There was no clinical or biochemical evidence of any adverse drug reaction during the study period.

A case report of a 28-year-old woman with atopic eczema who experienced two episodes of hepatitis described how the woman developed acute liver failure following the second episode and died, despite having had a liver transplant.[475] The mixture she had used included two plant components (*Dictamnus dasycarpus* and *Paeonia* species) that were also contained in mixtures used by two women described in a case series. The women suffered acute hepatic illness after using traditional Chinese herbs.[476] Both women recovered fully.

At least six cases of hepatotoxicity, one of cardiomyopathy and two of renal failure have been associated with the use of Chinese herbs for atopic eczema.[477–479] In 1999, aristolochic acid derived from *Aristolochia manshuriensis* (named Mutong) was cited as the cause of renal failure in two women undertaking long-term Chinese herbal medicine for atopic eczema. Mutong is a common ingredient in Chinese therapies for atopic eczema and can also be derived from species of *Akebia* and *Clematis* which do not contain aristolochic acid. Soon after this report was published, *Aristolochia* species were banned in the UK.

Safety issues have also been raised concerning the adulteration of Chinese herbal treatments for childhood eczema with conventional medication.[480] One letter described two case reports of children that had presented at clinic with improved atopic eczema symptoms following treatment with 'herbal' creams. In one case the product was found to contain 0.75 mg tablets of dexamethasone acetate and the other a potent topical corticosteroid.

Eleven Chinese herbal creams obtained from patients attending general and paediatric dermatology outpatient clinics were analysed and eight were found to contain dexamethasone at a mean concentration of 456 µg/g (range 64–1500 µg/g). All had been applied to areas of sensitive skin such as the face or flexures.[481]

In addition, some traditional herbal creams from Africa and Asia, such as Wau Wau cream and Abido cream, have also been found to contain potent topical steroids. Twenty-four 'herbal' creams submitted by 19 patients attending a paediatric dermatology clinic for atopic eczema in Birmingham (median age 3.82 years, range 0.69–7.98 years) were screened for their content.[482] Reported sources of the creams included India, Pakistan, China and Tanzania either via UK-based herbalists/clinics, friends and family overseas or mail order. Seven labelled creams contained clobetasol propionate. Thirteen of 17 unnamed creams contained corticosteroids: clobetasol propionate (four), clobetasol propionate plus hydrocortisone (one), betamethasone valerate (two), clobetasone butyrate (three), hydrocortisone (one) and there was an unidentifiable corticosteroid in one. Five creams of the same brand contained approximately 20% proprietary clobetasol propionate cream in a paraffin base. In all cases, the parents were unaware that the creams contained topical corticosteroids.

In 2002, the MHRA stated that adulteration of herbal creams with corticosteroids for various skin conditions continued to be a significant problem in the UK and as a result issued a warning to the public.[483] In January 2005, the MHRA reported that since 2002 the agency had investigated 17 suspected cases of illegal inclusion of corticosteroids in reportedly herbal creams, and of these seven were found to contain corticosteroids.[483]

Hypnotherapy

In one RCT, children with inadequately controlled atopic eczema were randomised to relaxation using hypnotherapy (focused on reducing itching), relaxation using biofeedback (no imagery included) or discussion with a psychologist (no instruction in specific techniques) for four 30 minute sessions 2, 3, 5 and 8 weeks after enrolment (n = 44, 31 analysed, age range 5–15 years).[484] [EL = 1–] Four were receiving treatment with long-term oral corticosteroids. Children were stabilised on topical and oral treatments. After 20 weeks' follow-up, changes in erythema, surface damage and lichenification were measured. Data from the two relaxation groups (hypnotherapy and biofeedback) showed a significant reduction from baseline in the severity of surface damage with time (P = 0.046) and of lichenification at 20 weeks (P = 0.02). There were no improvements over time in the discussion group.

Two case series investigated the use of hypnotherapy for atopic eczema.[485,486] [EL = 3] The first involved a group of 11 children (age range 5–12 years) with established atopic eczema.[485] After an initial control period, self-hypnosis was taught by a guided imagery technique with the aim of relieving itch and discomfort, and aiding relaxation. Over an 18 week period, atopic eczema was assessed by a doctor using an eczema score (maximum score 18) at six visits. The mean total eczema score decreased between most visits during the study with the median difference between visits 3 and 6 estimated to be 2.6, but this was not statistically significant (P = 0.139). In the second case series, 20 children (age range 2–15 years) with severe resistant atopic eczema were treated with hypnosis.[486] Treatment consisted of an individualised tape of 'Magic Music' incorporating the elements of relaxation, stress management, ego strengthening, skin comfort and post-hypnotic suggestions via a 5–10 minute story metaphor with a further 5–10 minutes of

music. Children and/or adults were asked to use the tapes nightly until the next clinic. Assessments of atopic eczema were made at three consecutive clinic appointments. All but one child showed immediate improvement which was maintained over the next two visits. A questionnaire was sent to the patients 18 months after receipt of the tape. Of the 12 responses to the questionnaire, ten children had maintained improvement in itching, scratching and sleep disturbance, and seven reported improvements in mood. Pictorial data only were presented in the paper. [EL = 3]

No safety data were identified for hypnotherapy.

Massage

One RCT considered massage therapy in young children with atopic eczema who were receiving standard care (mainly emollients and topical corticosteroids; *n* = 20, aged 2–8 years).[487] [EL = 1−] A 20 minute massage with emollient was given by their parents and compared with standard care only for 1 month. Over the 1 month period, parents of massaged children reported lower anxiety levels in their children and children improved significantly on all clinical measures including erythema, scaling, lichenification, excoriation and pruritus. The control group only improved significantly on the scaling measure. No between-group analysis was undertaken.

No safety data were identified for massage therapy.

Aromatherapy

An RCT on the effect of aromatherapy in childhood atopic eczema involved 16 children who were randomised to either counselling plus massage using essential oils or counselling with massage using base oil only.[488] [EL = 1−] Massage was performed by both therapist (weekly) and mothers (daily) for 8 weeks. Parents assessed daytime irritation score, night-time disturbance scores and general improvement scores. The results showed a statistically significant improvement of atopic eczema in both groups, but no intergroup differences. Post-trial continuation of aromatherapy treatments suggested that prolonged use of essential oils might cause allergic and irritant contact dermatitis.

Honey, beeswax and olive oil mixture

One controlled single-blind study evaluated a honey, beeswax and olive oil mixture for moderate to severe atopic eczema.[489] [EL = 2−] The study included 21 children (aged 5–16 years) of which ten were receiving no treatment on entry to the study (group 1) and 11 were using topical betamethasone esters (group 2). In group 1, lesions were treated with Vaseline® on the right side of the body and honey mixture on the left side. Both treatments were applied three times daily for 2 weeks. In group 2, skin lesions on the right side of the body were treated with betamethasone esters 0.1% and Vaseline (v/v 1:1) and those on the left side were treated with honey mixture and topical corticosteroid ointment (v/v 1:1). The main form of assessment was symptom scores at weeks 1 and 2 although at week 2 treatments were reassessed before continuing for a total of 6 weeks with a further reassessment of treatments at 4 weeks. In the honey mixture group, 8/10 children showed improvement after 2 weeks and 5/11 children pre-treated with betamethasone esters showed no deterioration upon a 75% reduction of topical corticosteroid doses (post-trial weeks 2–6) with honey mixture.

Nigella sativa *(black seed) oil*

One placebo-controlled double-blind RCT and one open-label study (reported in the same paper) investigated the effect of *Nigella sativa* (black seed) oil in patients with allergic diseases.[490] [EL = 1− and EL = 3, respectively] The RCT involved a total of 63 patients (aged 6–17 years) of whom nine had atopic eczema.[490] [EL = 1−] Treatment with black seed oil capsules (40–80 mg/kg/day) was compared with treatment with placebo oil capsules. Both treatments were taken three times daily for 8 weeks. Clinical improvement (patients' subjective evaluation) occurred in 2/6 patients on black seed oil compared with 1/3 patients in the placebo group. No other clinical data were reported. The open-label study involved a total of 49 patients (aged 6–15 years) of whom six had atopic eczema.[490] [EL = 3] All patients took two capsules of black seed oil, three times daily for 6–8 weeks. It was reported that 3/6 patients had subjective improvement of clinical symptoms, 2/6 remained unchanged and 1/6 had deterioration. Gastrointestinal adverse events were noted in 18% of participants.

Gamma linolenic acid

Four double-blind placebo-controlled RCTs investigated the effects of gamma linolenic acid on atopic eczema in children. Three of these trials involved evening primrose oil and the other involved borage oil (both sources of gamma linolenic acid). The first RCT involved children aged 2–4 years (n = 24) who received six 0.5 g evening primrose oil capsules or six 0.5 g placebo (olive oil) capsules daily for 4 weeks.[491] [EL = 1+] After 4 weeks the total eczema score (incorporating signs and symptoms of eczema) improved significantly in children taking evening primrose oil (P < 0.01). Placebo-treated children's clinical status remained largely unchanged.[491]

In the second RCT, children aged 7–12 years were randomised to receive evening primrose oil (six capsules of 500 mg) and fish oil (six capsules of 107 mg), or placebo (six capsules of olive oil) daily for 16 weeks (n = 62).[65] [EL = 1+] Disease activity was monitored by clinical severity scores recorded by the investigator, topical corticosteroid requirement and symptom scores recorded by participants. The study also included adults, and the children's data were not analysed separately. No improvement with active treatment was observed.[65]

In the third RCT, two doses of evening primrose oil (0.5 g/kg/day or 50% mix of 0.5 g/kg and placebo) were tested against placebo capsules (olive oil) in children (n = 51, mean age 4.2 years).[492] [El=1+] After 8 weeks' treatment a significant improvement in the overall severity of the clinical condition (assessed using the total eczema score) was seen in children treated with the high dose of evening primrose oil (high dose versus placebo, mean difference 0.56, P = 0.046) independently of whether the children had manifestations of IgE-mediated allergy. However, there was no significant improvement in the overall severity of the clinical condition in children treated with the low dose of evening primrose oil (low dose versus placebo, mean difference 0.51, P = 0.077). [492]

None of the three RCTs of evening primrose oil reported any safety data.[65,491,492]

One placebo-controlled RCT investigated the effectiveness and tolerability of borage oil in children and adults with atopic eczema (n = 140)[493] [EL = 1+] Sixty-nine children received two capsules twice daily (460 mg gamma linolenic acid), for 12 weeks. Data for children were not reported separately. At 12 weeks, the difference in mean improvements in SASSAD severity scores between the two groups was 1.4 (95% CI −2.2 to 5.0), indicating a non-significant benefit of placebo (P = 0.45). No significant differences were observed between treatment groups in the other assessments (symptom scores assessed on visual analogue scales, topical corticosteroid requirement, global assessment of response, adverse events and tolerability). Separate analysis of children's and adults' data did not indicate any difference in response. The treatments were well tolerated.

In 2002 the MHRA (then the Medicines Control Agency) withdrew the product licences (marketing authorisations) for two major evening primrose oil preparations because there was insufficient evidence for their effectiveness as medicines for treating atopic eczema.[494] No concerns were expressed about safety and evening primrose oil is still available as a dietary supplement.

Cost-effectiveness

No cost-effectiveness analyses were identified, but two studies reported the costs of complementary therapies. One US study published in 1998 reported the cost of massage ($30), but did not link this with clinical outcomes.[487] The other study provided an analysis of cost associated with homeopathy versus conventional therapy in Germany.[495] Since this was not a UK study it is of limited relevance to the NHS setting. The cost analysis did not distinguish between children and adults or present the analysis by diagnosis. Resource use data on current health service use and use in the previous year were obtained for a subgroup of 38% of patients. Homeopathy accounted for 10% of overall costs, and the costs did not vary significantly between groups. However, the methods of analysis of the cost data were neither conventional nor fully explained.

Evidence statement for complementary therapies

Despite the popularity of complementary therapies for atopic eczema in children there was a lack of clinical effectiveness, cost-effectiveness and safety data. The few studies that were available on homeopathy, Chinese herbal medicine, massage, hypnotherapy and aromatherapy were of poor quality, and in some cases included adults as well as children. The evidence relating to

gamma linolenic acid taken in the form of evening primrose oil or borage oil suggested that it was not an effective treatment for atopic eczema. There were significant safety concerns with some complementary therapies: some traditional herbal creams were found to contain topical corticosteroids and some Chinese herbal medicines were linked to renal damage and hepatotoxicity.

From evidence to recommendations

There was insufficient evidence for any of the complementary therapies described here to make recommendations for their use in clinical practice. The GDG noted some potential benefits of the therapies considered and identified a need for further research. Despite the lack of evidence, homeopathy is already available within the NHS. Treatments with Chinese herbal medicine showed positive outcomes although there were safety issues to be considered. Some traditional Chinese herbal medicines have been associated with liver damage and even death. In addition, serious adverse events have arisen as a result of adulteration, foreign language labelling and taxonomical errors of herbal mixtures. The evidence for massage was promising, with emollients being the optimal vehicle for application. Gamma linolenic acid supplementation was shown to be safe and some patients may feel it is of benefit despite the lack of clinical evidence.

Given the public's concern about the safety of conventional treatments for atopic eczema (which may lead them to consider complementary therapies) it is important that the public understands that 'natural' remedies are not necessarily safe and that some complementary therapies are potentially harmful. It is also important that appropriately designed RCTs are conducted to evaluate the effectiveness, cost-effectiveness and safety of complementary therapies for the treatment of atopic eczema in children.

Recommendations for complementary therapies (including research recommendations) are presented in Section 7.11.

7.10 Behavioural therapies

Behavioural therapy is aimed at habit reversal. In atopic eczema, behavioural therapy attempts to break the itch–scratch cycle.

The HTA on atopic eczema treatments found limited data for psychological treatments.[26] The studies that were included investigated behavioural management (habit reversal), relaxation and cognitive behavioural therapies and were conducted in adults.[26]

No published studies evaluating the effects of habit reversal in children with atopic eczema were identified.

One controlled trial investigated the effectiveness of cognitive behavioural-based stress management training for children aged 8–16 years with atopic eczema (n = 60).[496] [EL = 2−] The trial evaluated a patient education programme implemented during inpatient rehabilitation in a German hospital setting. The average SCORAD index at the start of the study was 37.80 (SD 15.54). Children either took part in a multi-modal patient education programme or standard patient education training. The multi-modal programme was implemented in the setting of inpatient rehabilitation and consisted of ten 1–hour training sessions. Four sessions consisted of standard patient education and the remaining six comprised components of 'anti-stress training' in which cognitive behavioural techniques were used to modify the patients' stress and disease management. The control group received standard education over six sessions. The outcome measures were the SCORAD index and the German coping questionnaire for children and adolescents (Stressverarbeitungsfragebogen, SVF-KJ) applied at baseline, 1 month and 6 months. Immediately after rehabilitation, both groups showed a significant reduction in disease severity (SCORAD index, $P \leq 0.001$). At the 6 month assessment, there were only 44 datasets (experimental n = 25, control n = 19). The data suggested that the cognitive behavioural-based educational programme led to improvements in subjective health perception and ability to cope with common stressors. In contrast, the control group tended to cope less well with stress in the long-term.[496]

Educational interventions have also been used to bring about behavioural change through health education of parents of children with atopic eczema.[497] Education for children with atopic eczema and their parents/carers is discussed in Section 8.1.

Cost-effectiveness

No studies that addressed the cost-effectiveness of behavioural therapy for children with atopic eczema were identified.

Evidence statement for behavioural therapies

There were no good-quality data regarding the effectiveness or cost-effectiveness of behavioural therapy in children with atopic eczema.

From evidence to recommendations

There was insufficient evidence of effectiveness or cost-effectiveness of behavioural therapy for the GDG to make a recommendation.

Research recommendations for behavioural therapy are presented in Section 7.11.

7.11 Recommendations for treatment

Recommendations for stepped approach to management

Healthcare professionals should use a stepped approach for managing atopic eczema in children. This means tailoring the treatment step to the severity of the atopic eczema. Emollients should form the basis of atopic eczema management and should always be used, even when the atopic eczema is clear. Management can then be stepped up or down, according to the severity of symptoms, with the addition of the other treatments listed in Table 7.4.

Table 7.4 Treatment options

Mild atopic eczema	Moderate atopic eczema	Severe atopic eczema
Emollients	Emollients	Emollients
Mild potency topical corticosteroids	Moderate potency topical corticosteroids	Potent topical corticosteroids
	Topical calcineurin inhibitors	Topical calcineurin inhibitors
	Bandages	Bandages
		Phototherapy
		Systemic therapy

Healthcare professionals should offer children with atopic eczema and their parents or carers information on how to recognise flares of atopic eczema (increased dryness, itching, redness, swelling and general irritability). They should give clear instructions on how to manage flares according to the stepped-care plan, and prescribe treatments that allow children and their parents or carers to follow this plan.

Treatment for flares of atopic eczema in children should be started as soon as signs and symptoms appear and continued for approximately 48 hours after symptoms subside.

Research recommendations for stepped approach to management

How should flares of atopic eczema be defined/recognised, what pattern do they take and how useful is this to clinical practice?

Why this is important
Atopic eczema is an episodic disease punctuated by flares and remissions in most cases. It is important to be able to recognise the onset of a flare for children and their parents so that treat-

ment can be given promptly and effectively thus improving quality of life and care. It would also aid decisions on clinical treatment strategies and provide an effective outcome measure for research purposes.

Which are the best, most cost-effective treatment strategies for managing and preventing flares in children with atopic eczema?

Why this is important
Atopic eczema is usually an episodic disease of exacerbation (flares) and remissions, except for severe cases where it may be continuous (2–6% of cases). Flares may occur as frequently as two or three times per month and have a very negative effect on quality of life. They are time-consuming and expensive to treat. There is limited evidence suggesting that strategies to prevent flares can reduce the number, frequency and severity of flares and the amount of treatment required. Identifying good strategies would improve patient care and quality of life, and free up NHS resources. Strategies that could be considered in this research include continuous versus intermittent topical treatments or combinations of products such as topical corticosteroids and topical calcineurin inhibitors.

What effect does improving the control of atopic eczema in the first year of life have on the long-term control and severity of atopic eczema and the subsequent development and severity of food allergy, asthma and allergic rhinitis?

Why this is important
Uncontrolled atopic eczema in children may progress to chronic disease involving the production of auto-immune antibodies to the skin. Early intervention to restore the defective skin barrier might alter the course of atopic eczema by preventing allergen penetration. A systematic review is needed to evaluate the available evidence on these factors. The results should feed in to the design of a large randomised controlled trial investigating the long-term effect of controlling atopic eczema in the first year of life. Early effective treatment to control atopic eczema and the development of other atopic conditions would be extremely cost-effective, have a major impact on service provision and improve the quality of life of children with atopic eczema and their parents and carers.

Recommendations for emollients

Healthcare professionals should offer children with atopic eczema a choice of unperfumed emollients to use every day for moisturising, washing and bathing. This should be suited to the child's needs and preferences, and may include a combination of products or one product for all purposes. Leave-on emollients should be prescribed in large quantities (250–500 g weekly) and easily available to use at nursery, pre-school or school.

Healthcare professionals should inform children with atopic eczema and their parents or carers that they should use emollients in larger amounts and more often than other treatments. Emollients should be used on the whole body both when the atopic eczema is clear and while using all other treatments.

Healthcare professionals should inform children with atopic eczema and their parents or carers that they should use emollients and/or emollient wash products instead of soaps and detergent-based wash products.

Healthcare professionals should advise parents or carers of children aged under 12 months with atopic eczema to use emollients and/or emollient wash products instead of shampoos for the child. If shampoo is used for older children with atopic eczema it should be unperfumed and ideally labelled as being suitable for eczema; washing the hair in bath water should be avoided.

Healthcare professionals should show children with atopic eczema and their parents or carers how to apply emollients, including how to smooth emollients onto the skin rather than rubbing them in.

Healthcare professionals should offer an alternative emollient if a particular emollient causes irritation or is not acceptable to a child with atopic eczema.

Healthcare professionals should review repeat prescriptions of individual products and combinations of products with children with atopic eczema and their parents or carers at least once a year to ensure that therapy remains optimal.

Where emollients (excluding bath emollients) and other topical products are used at the same time of day to treat atopic eczema in children, the different products should ideally be applied one at a time with several minutes between applications where practical. The preferences of the child and parents or carers should determine which product should be applied first.

Research recommendations for emollients

Which are the most effective and cost-effective combinations of emollient products to use for the treatment of childhood atopic eczema?

Why this is important
Most children with atopic eczema have a very dry skin and early treatment with emollients makes the skin less itchy, reducing the severity of the eczema. There are numerous types and formulations of emollients but little data to suggest how they can best be used in the most effective and cost-effective way.

Does the regular use of emollients reduce the severity and frequency of flares and the need for other topical agents in the treatment of atopic eczema in children?

Why this is important
Clinical consensus suggests that this is the case but there is little good evidence for this. Confirmation would help to encourage children and their parents to comply with therapy and reduce the need for other therapies, as well as improve their quality of life.

Recommendations for topical corticosteroids

Healthcare professionals should discuss the benefits and harms of treatment with topical corticosteroids with children with atopic eczema and their parents or carers, emphasising that the benefits outweigh possible harms when they are applied correctly.

The potency of topical corticosteroids should be tailored to the severity of the child's atopic eczema, which may vary according to body site. They should be used as follows:

- use mild potency for mild atopic eczema
- use moderate potency for moderate atopic eczema
- use potent for severe atopic eczema
- use mild potency for the face and neck, except for short-term (3–5 days) use of moderate potency for severe flares
- use moderate or potent preparations for short periods only (7–14 days) for flares in vulnerable sites such as axillae and groin
- do not use very potent preparations in children without specialist dermatological advice.

It is recommended that topical corticosteroids for atopic eczema should be prescribed for application only once or twice daily.*

It is recommended that where more than one alternative topical corticosteroid is considered clinically appropriate within a potency class, the drug with the lowest acquisition cost should be prescribed, taking into account pack size and frequency of application.*

* These recommendations are taken from 'Frequency of application of topical corticosteroids for atopic eczema' (NICE technology appraisal guidance 81). They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

Healthcare professionals should inform children with atopic eczema and their parents or carers that they should only apply topical corticosteroids to areas of active atopic eczema (or eczema that has been active within the past 48 hours), which may include areas of broken skin.

Healthcare professionals should exclude secondary bacterial or viral infection if a mild or moderately potent topical corticosteroid has not controlled the atopic eczema within 7–14 days. In children aged 12 months or over, potent topical corticosteroids should then be used for as short a time as possible and in any case for no longer than 14 days. They should not be used on the face or neck. If this treatment does not control the atopic eczema, the diagnosis should be reviewed and the child referred for specialist dermatological advice.

Potent topical corticosteroids should not be used in children aged under 12 months without specialist dermatological supervision.

Healthcare professionals who dispense topical corticosteroids should apply labels stating the potency class of the preparations to the container (for example, the tube), not the outer packaging.

Healthcare professionals should consider treating problem areas of atopic eczema with topical corticosteroids for two consecutive days per week to prevent flares, instead of treating flares as they arise, in children with frequent flares (two or three per month), once the eczema has been controlled. This strategy should be reviewed within 3–6 months to assess effectiveness.

A different topical corticosteroid of the same potency should be considered as an alternative to stepping up treatment if tachyphylaxis to a topical corticosteroid is suspected in children with atopic eczema.

Research recommendations for topical corticosteroids

What are the long-term effects (when used for between 1 and 3 years) of typical use of topical corticosteroids in children with atopic eczema?

Why this is important
Around 70–80% of parents and carers of children with atopic eczema are concerned about the side effects of topical corticosteroids and this often prevents adherence to therapy (at least 25% of parents and carers report non-usage because of anxiety). Despite the fact that topical corticosteroids have been in clinical use since 1962, there are limited data on their long-term effects (greater than a few weeks) on skin thickness, hypothalamic–pituitary–adrenal (HPA) axis suppression and other side effects. Clinical consensus suggests that long-term usage, within clinically recommended dosages, appears to be safe; research confirming this would greatly improve adherence to therapy and clinical outcomes, and reduce parental anxiety. The research could include comparisons between children who use topical corticosteroids for shorter and longer periods, and with those who use other topical preparations such as emollients and topical calcineurin inhibitors.

What are the optimal treatment regimens for using topical corticosteroids in the treatment of atopic eczema in children?

Why this is important
Topical corticosteroids have been used since 1962, which predated modern randomised controlled trials (RCTs). High-quality comparative RCTs are required to provide data on the effectiveness and cost-effectiveness of various topical corticosteroids preparations in the treatment of atopic eczema in children.

Recommendations for topical calcineurin inhibitors

Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity.*

Topical tacrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged 2 years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.*

Pimecrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged 2–16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.*

For the purposes of this guidance, atopic eczema that has not been controlled by topical corticosteroids refers to disease that has not shown a satisfactory clinical response to adequate use of the maximum strength and potency that is appropriate for the patient's age and the area being treated.*

It is recommended that treatment with tacrolimus or pimecrolimus be initiated only by physicians (including general practitioners) with a special interest and experience in dermatology, and only after careful discussion with the patient about the potential risks and benefits of all appropriate second-line treatment options.*

Healthcare professionals should explain to children with atopic eczema and their parents or carers that they should only apply topical calcineurin inhibitors to areas of active atopic eczema, which may include areas of broken skin.

Topical calcineurin inhibitors should not be used under occlusion (bandages and dressings) for treating atopic eczema in children without specialist dermatological advice.

For facial atopic eczema in children that requires long-term or frequent use of mild topical corticosteroids, consider stepping up treatment to topical calcineurin inhibitors.

Research recommendations for topical calcineurin inhibitors

What are the most effective, cost-effective and safe ways of using combinations of topical calcineurin inhibitors with topical corticosteroids of different potencies in the treatment of atopic eczema in children, with particular reference to areas of thin skin such as the face and flexures?

Why this is important

Topical calcineurin inhibitors and topical corticosteroids are often combined in clinical practice but high-quality data are required on their safety and effectiveness/cost-effectiveness in terms of clinical benefit.

What is the effectiveness and safety of using topical calcineurin inhibitors for treating children with atopic eczema in comparison with using different potencies of topical corticosteroids and does this differ in various body sites such as the face?

Why this is important

There are few direct comparative data on the use of topical calcineurin inhibitors, particularly pimecrolimus, in different body sites and in comparison with topical corticosteroids of different potencies. Long-term use of hydrocortisone on the face is more likely to cause cutaneous atrophy than when used in other sites and topical pimecrolimus appears to be a suitable alternative. High-quality RCTs would help to answer this question.

How effective/cost-effective and safe is the use of topical tacrolimus 0.1% ointment for treating children with atopic eczema?

Why this is important

At present topical tacrolimus 0.1% ointment is not licensed for use in children under 16 years. However, clinical consensus suggests that it may be a useful, safer and probably more cost-

* These recommendations are taken from 'Tacrolimus and pimecrolimus for atopic eczema' (NICE technology appraisal guidance 82). They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

effective alternative to, for example, long-term potent topical corticosteroids or systemic therapies for children with chronic eczema unresponsive to the 0.03% preparation of topical tacrolimus. High-quality RCTs and safety studies are required to answer this question.

What are the optimal treatment durations when using topical pimecrolimus and tacrolimus in the treatment of children with atopic eczema?

Why this is important
The topical calcineurin inhibitor formulations are new and relatively expensive with optimal treatment duration strategies not yet established. High-quality RCTs would lead to more effective/cost-effective therapy and a better use of scarce resources.

How safe are topical calcineurin inhibitors for long-term therapy (1–3 years) in the treatment of atopic eczema in children?

Why this is important
Topical calcineurin inhibitors are new drugs and safety for longer term use is not yet established. Adequately powered long-term studies in relation to tacrolimus and pimecrolimus are needed.

Recommendations for dry bandages and medicated dressings (including wet wrap therapy)

Occlusive medicated dressings and dry bandages should not be used to treat infected atopic eczema in children.

Localised medicated dressings or dry bandages can be used with emollients as a treatment for areas of chronic lichenified (localised skin thickening) atopic eczema in children.

Localised medicated dressings or dry bandages with emollients and topical corticosteroids can be used for short-term treatment of flares (7–14 days) or areas of chronic lichenified atopic eczema in children.

Whole-body (limbs and trunk) occlusive dressings (including wet wrap therapy) and whole-body dry bandages (including tubular bandages and garments) should not be used as first-line treatment for atopic eczema in children and should only be initiated by a healthcare professional trained in their use.

Whole-body (limbs and trunk) occlusive dressings (including wet wrap therapy) with topical corticosteroids should only be used to treat atopic eczema in children for 7–14 days (or for longer with specialist dermatological advice), but can be continued with emollients alone until the atopic eczema is controlled.

Research recommendations for dry bandages and medicated dressings (including wet wrap therapy)

What are the benefits and harms of the different bandaging therapies (for example, wet, dry and medicated bandages) in the treatment of atopic eczema in children?

Why this is important
Bandages are widely used to treat atopic eczema in children and many different treatment regimens are used. These treatments are expensive and time-consuming but there are few data on their clinical and cost-effectiveness and safety. Good-quality RCTs are required to evaluate benefits and harms, in particular which children benefit from such therapy and how therapies should be used.

How effective, cost-effective and safe are wet wrap dressings with emollients alone or in combination with various potencies of topical corticosteroids, for the longer term management (greater than 5 days consecutively) of atopic eczema in children and how do they compare with the use of other topical therapies alone?

Why this is important
Wet wrap dressings, usually combined with topical corticosteroid preparations, can be very effective for short-term treatment of severe eczema, but because they increase steroid absorption there is a significant risk of HPA axis suppression after 5 days' use and an increased risk of skin infection. In clinical practice they are frequently used for periods longer than 5 days, with emollients alone or in combination with topical corticosteroids, often diluted. It is not known how safe, effective/cost-effective or practical they are for longer term management in comparison with using topical treatments alone.

How effective is the use of topical corticosteroids of different potencies or topical calcineurin inhibitors under occlusion for the treatment of atopic eczema in children and, if effective, for how long can they safely be used?

Why this is important
Occlusion increases absorption of a drug but this also increases the systemic effects. Increasing the effectiveness may compromise safety, particularly if a large surface area is involved. Such research would help to ascertain safety and efficacy of occlusion, particularly in the case of the topical calcineurin inhibitors, where there are no clinical data and little clinical experience of such use.

Recommendations for antihistamines and other antipruritics

Oral antihistamines should not be used routinely in the management of atopic eczema in children.

Healthcare professionals should offer a 1 month trial of a non-sedating antihistamine to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria. Treatment can be continued, if successful, while symptoms persist, and should be reviewed every 3 months.

Healthcare professionals should offer a 7–14 day trial of an age-appropriate sedating antihistamine to children aged 6 months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers. This treatment can be repeated during subsequent flares if successful.

Research recommendations for antihistamines and other antipruritics

What is the clinical effectiveness, cost-effectiveness and safety of using sedating and non-sedating antihistamines in children with atopic eczema in terms of the outcomes itch and night-time sleep disturbance?

Why this is important
Antihistamines are frequently used to reduce itching and as night-time sedation for younger children with atopic eczema, often to allow parents some sleep. In school-age children the non-sedating antihistamines are sometimes used to reduce daytime itch. There are no data to support the use of antihistamines as an effective clinical strategy. However, lack of data does not mean lack of efficacy and some children describe them as helpful in reducing itch and improving sleep. This is a cost issue and important from clinical and patient perspectives.

Recommendations for treatments for infections associated with atopic eczema in children

Children with atopic eczema and their parents or carers should be offered information on how to recognise the symptoms and signs of bacterial infection with staphylococcus and/or streptococcus (weeping, pustules, crusts, atopic eczema failing to respond to therapy, rapidly worsening atopic eczema, fever and malaise). Healthcare professionals should provide clear

information on how to access appropriate treatment when a child's atopic eczema becomes infected.

Children with atopic eczema and their parents or carers should be informed that they should obtain new supplies of topical atopic eczema medications after treatment for infected atopic eczema because products in open containers can become contaminated with microorganisms and act as a source of infection.

Healthcare professionals should only take swabs from infected lesions of atopic eczema in children if they suspect microorganisms other than *Staphylococcus aureus* to be present, or if they think antibiotic resistance is relevant.

Systemic antibiotics that are active against S*taphylococcus aureus* and streptococcus should be used to treat widespread bacterial infections of atopic eczema in children for 1–2 weeks according to clinical response.

Flucloxacillin should be used as the first-line treatment for bacterial infections in children with atopic eczema for both *Staphylococcus aureus* and streptococcal infections. Erythromycin should be used in children who are allergic to flucloxacillin or in the case of flucloxacillin resistance. Clarithromycin should be used if erythromycin is not well tolerated.

The use of topical antibiotics in children with atopic eczema, including those combined with topical corticosteroids, should be reserved for cases of clinical infection in localised areas and used for no longer than 2 weeks.

Antiseptics such as triclosan or chlorhexidine should be used, at appropriate dilutions, as adjunct therapy to decrease bacterial load in children who have recurrent infected atopic eczema. Long-term use should be avoided.

Healthcare professionals should consider infection with herpes simplex (cold sore) virus if a child's infected atopic eczema fails to respond to treatment with antibiotics and an appropriate topical corticosteroid.

If a child with atopic eczema has a lesion on the skin suspected to be herpes simplex virus, treatment with oral aciclovir should be started even if the infection is localised.

If eczema herpeticum (widespread herpes simplex virus) is suspected in a child with atopic eczema, treatment with systemic aciclovir should be started immediately and the child should be referred for same-day specialist dermatological advice. If secondary bacterial infection is also suspected, treatment with appropriate systemic antibiotics should also be started.

If eczema herpeticum involves the skin around the eyes, the child should be treated with systemic aciclovir and should be referred for same-day ophthalmological and dermatological advice.

Children with atopic eczema and their parents or carers should be offered information on how to recognise eczema herpeticum. Signs of eczema herpeticum are:

- areas of rapidly worsening, painful eczema
- clustered blisters consistent with early-stage cold sores
- punched-out erosions (circular, depressed, ulcerated lesions) usually 1–3 mm that are uniform in appearance (these may coalesce to form larger areas of erosion with crusting)
- possible fever, lethargy or distress.

Research recommendations for infections associated with atopic eczema in children

What are the prevalence and patterns of antibiotic resistance in children with atopic eczema and how clinically meaningful are these in terms of clinical management and the emergence of multiresistant bacteria?

Why this is important
Up to 80% of children with atopic eczema are known to harbour *Staphylococcus aureus*, although this may not be clinically apparent. There are data to show that there is an increasing

resistance (up to 66% of cultures in some UK regions) to antibiotics such as fusidic acid, which is commonly used as a topical agent to treat infected eczema. It is not clear how important this is in clinical practice and what danger it poses to society as a whole. Much more information is required to determine the pattern and emergence of resistant strains and their relationship to the use of topical antibiotics.

How should bacterially infected atopic eczema in children be defined, how should it be treated and for how long? What are the indications for use of antimicrobial agents in terms of their clinical effectiveness (including palatability), cost-effectiveness and safety?

Why this is important
Bacterial colonisation of atopic eczema in children is common (up to 80% of cases) but not all will develop clinically manifest infection. However, secondary infection is a common cause of flares of eczema and is often unrecognised by healthcare professionals and parents/carers. Unnecessary use of antibiotics is expensive and potentially dangerous (in terms of systemic effects, development of allergy and emergence of multiresistant strains of microorganisms). Information from research is required to enable clear treatment plans to be made about when and for how long to use antimicrobial agents and which agents are the safest and most suitable for different ages of child.

Recommendations for phototherapy and systemic treatments

Healthcare professionals should consider phototherapy or systemic treatments for the treatment of severe atopic eczema in children when other management options have failed or are inappropriate and where there is a significant negative impact on quality of life. Treatment should be undertaken only under specialist dermatological supervision by staff who are experienced in dealing with children.

Phototherapy or systemic treatments should only be initiated in children with atopic eczema after assessment and documentation of severity of atopic eczema and quality of life.

Research recommendations for phototherapy and systemic treatments

How effective, cost-effective and safe is phototherapy in children with severe atopic eczema? How and when should it be used and should it be combined with other topical therapies?

Why this is important
Phototherapy is often used for children with severe atopic eczema but there are few studies reporting on its effectiveness, cost-effectiveness and long-term safety. High-quality RCTs are needed which should include comparisons with different types of phototherapy and in combination with different topical therapies.

How effective, cost-effective and safe are systemic treatment options in children with severe atopic eczema and how and when should they be used? For example: azathioprine, ciclosporin, methotrexate, mycophenolate mofetil, oral prednisolone and the newer biological agents.

Why this is important
Direct comparisons of the effectiveness of the systemic treatment options in children with severe atopic eczema are required, focusing on quality of life and long-term safety. All these treatment strategies are currently unlicensed for use in children under 12 years of age and should be restricted to specialist use.

Recommendations for complementary therapies

Children with atopic eczema and their parents or carers should be informed that the effectiveness and safety of complementary therapies such as homeopathy, herbal medicine, massage

and food supplements for the management of atopic eczema have not yet been adequately assessed in clinical studies.

Children with atopic eczema and their parents or carers should be informed that:

- they should be cautious with the use of herbal medicines in children and be wary of any herbal product that is not labelled in English or does not come with information about safe usage*
- topical corticosteroids are deliberately added to some herbal products intended for use in children with atopic eczema*
- liver toxicity has been associated with the use of some Chinese herbal medicines intended to treat atopic eczema.

Children with atopic eczema and their parents or carers should be asked to inform their health-care professionals if they are using or intend to use complementary therapies.

Children with atopic eczema and their parents or carers should be informed that if they plan to use complementary therapies, they should keep using emollients as well.

Children with atopic eczema and their parents or carers should be advised that regular massage with emollients may improve the atopic eczema.

Research recommendation for complementary therapies

How effective, cost-effective and safe are complementary therapies for the management of atopic eczema in children and how do they compare with conventional Western therapies?

Why this is important
There are almost no data on the effectiveness of complementary treatment for children with atopic eczema, although there are some data to suggest that up to 60% of parents have tried these. High-quality RCTs are needed which should include comparisons with placebo controls and different forms of conventional and complementary medicine, used alone or in combination with each other. This will aid patient and physician choice and answer many unanswered questions. It has potential cost and licensing implications.

Research recommendations for behavioural therapies

Are behavioural and psychological interventions, for example habit reversal techniques, effective in the management of atopic eczema in children and would their use be feasible and cost-effective in clinical practice?

Why this is important
There are data to show that atopic eczema can have a negative psychological effect on children and their family. Adults with atopic eczema admit that they 'habit scratch', which perpetuates the disease and this is often true for children as well. There are also quality of life data to suggest that atopic eczema is worse than having other chronic childhood diseases. However, there are almost no data examining the effects of psychological interventions to treat these effects. Access for psychological help in the NHS is currently very limited and waiting lists are long. Such research would help to utilise scarce resources effectively and assist future service planning.

* See 'Using herbal medicines: advice to consumers'. July 2006, MHRA, www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=661.

8 Education and adherence to therapy

8.1 Education

Education programmes for children with atopic eczema and their families aim to improve the management of the condition physically, psychologically and socially.

Studies considered in this section

RCTs evaluating the effects of education programmes are considered in this section. Studies of non-comparative design are also described.

Overview of available evidence

Three RCTs and two case series considered the effects of education programmes for children with atopic eczema and their families.

The largest RCT was conducted in Germany.[498] (Two earlier publications describing the same intervention in fewer children were also identified.[100,101] The children in these two studies were believed to be included in the largest RCT therefore these studies were not considered further.) The RCT evaluated a 6 week education programme for the management of moderate to severe atopic eczema in people aged 3 months to 18 years (n = 992).[498] The programme was age-related and structured, covering medical, nutritional and psychological issues, and was delivered as 2 hour once-weekly sessions by a multi-professional team. Overall, 17% of participants were lost to follow-up and were not included in the evaluation of results; the loss to follow-up was lower in the intervention group (10% versus 24%). At 1 year, improvements in severity of atopic eczema (SCORAD) in children who received the education programme were significantly greater than in the control group. Between-group differences were −5.2 (95% CI −8.2 to −2.2) for children aged 3 months to 7 years and −8.2 (95% CI −13.6 to −2.8) for those aged 8–12 years. Improvements in subjective severity (Skin Detectives Questionnaire) in these age groups were also significantly greater in the group who received education. Improvements in itching behaviour ('catastrophisation' (negative thoughts of pain that had got out of control) and coping) were significantly greater in the group receiving education. The parents of children aged under 7 years experienced an improvement in all five subscales of the FEN questionnaire. Parents of children aged 8–12 years experienced improvement in three of the five subscales (confidence in medical treatment, emotional coping, and acceptance of disease).[498] [EL = 1−]

The second RCT evaluated the effects of a nurse-led educational intervention for the parents of children with varying severity of atopic eczema (age range 4 months to about 6 years). The comparator was routine (standard) care (n = 50 randomised, 42 completed and analysed). The nurse-led education programme consisted of a 2 hour session covering general information about atopic eczema, environmental control, topical treatments (different types and how to use them), practical advice to aid self-management, importance of maintenance therapy, and expectations. After 4 months, there was a greater improvement in the condition of the atopic eczema in the intervention group (total atopic eczema score based on type, intensity and distribution of lesions fell by 78% compared with 62% in the standard group, $P < 0.05$). There was no difference between the groups in the decrease of itch score and the extent of atopic eczema. The amount of topically administered hydrocortisone (the strength was not reported) was significantly higher in children whose parents received nurse-led education than in those who did not ($P < 0.01$).[499] [EL = 1−]

The third RCT considered the effects of a 2 hour educational session for children with atopic eczema (age range 0–16 years, mean 4 years, *n* = 61) that covered the condition and its management (and included a practical session on wet wrapping and application of creams). At 12 weeks, reduction in severity (SCORAD) and improvement in CDLQI scores was significantly greater in the group who received education compared with the group receiving usual care. Changes in DFI and IDQoL scores were not significantly different between groups.[500] [EL = 1+]

One case series investigated the effect of informing families of 17 children with atopic eczema about the course of the disease. Six 2 hour group sessions were conducted at weekly intervals covering medical, psychological and behavioural issues of atopic eczema. Overall, 79% of families thought that the programme was 'satisfactory'; attitudes towards the disease were reported as 'more tranquil' in 79%; improvements were also reported in relations with the child (in 79%) and in communication with a partner (50%). Overall, 30% of families reported less frequent itching, and 43% reported a more stable sleep–waking rhythm.[88] [EL = 3]

The second case series (*n* = 50, age range 1–7 years) was a study of the effects of a one-off advice and demonstration session by a community pharmacist on the use of emollients. The study reported statistically significant reductions in itch and irritability as measured on a 0–10 scale.[501] [EL = 3]

8.2 Adherence to therapy

Adherence to treatment strategies is important in achieving desired outcomes in all areas of medicine, but is of particular importance in the self-management of atopic eczema owing to the relatively complicated and potentially time-consuming treatment strategies used.

Adherence to therapy is closely related to education of children with atopic eczema, their parents and/or caregivers, and the healthcare professionals who provide their care.

Studies considered in this section

Controlled trials evaluating interventions to improve adherence would have been considered here if any had been available. In the absence of such evidence, studies of any design that reported factors influencing adherence to therapy in children with atopic eczema were considered.

Overview of available evidence

Five studies investigated factors that affected adherence to therapy. Of these, four were surveys carried out in Japan, Australia and the UK, and in eight (unspecified) countries; the remaining study was a case series conducted in the UK.

Three of the surveys provided information about factors affecting adherence to topical corticosteroid therapy.[96,502,503] The first found that 57% of parents of children with atopic eczema believed that topical corticosteroids should be used only to treat severe atopic eczema, and that 20% of parents believed that topical corticosteroid creams were 'too dangerous' to use on their children (*n* = 109). 'Natural therapy' would have been preferred by 46% of parents, and 64% reported that some treatments stung or caused itching. The proportions of parents who reported that their children were sometimes or always uncooperative with treatment were 15% and 49%, respectively. Treatment was found to be 'always' too time-consuming by 7% of parents and 'sometimes' too time-consuming by 32%. Overall, 54% believed that treatment had failed because the condition relapsed.[502] [EL = 3]

The second survey of 142 parents of children with atopic eczema (and 58 adults) found that 73.2% of parents were worried about using topical corticosteroid creams and ointments on their child's skin. In 36.5% of the parents who had worries about topical corticosteroid creams, the worries stopped the parents from using the topical corticosteroids prescribed. The patient's age, gender, duration of atopic eczema and whether it was the patient's first visit or a follow-up visit had no effect on whether parents of children with atopic eczema or adults with atopic eczema worried about using topical corticosteroids or whether the worries stopped the use of the topical corticosteroids. The reasons given for fears about using topical corticosteroids by parents of children with atopic eczema and adults with atopic eczema were skin thinning, non-specific long-term effects, absorption/effects on growth and development, ageing/wrinkling, changes

in skin colour, making the atopic eczema worse, becoming immune to their effect, becoming dependent, scarring, stretchmarks, pain/stinging, reduced immunity to infections, cataracts, cancer, sunburn, bruising and increased body hair.[503] [EL = 3]

The third survey reported that 56% of caregivers (parents) of young children (aged 2–13 years) with atopic eczema were concerned about using topical corticosteroids (*n* = 779 caregivers surveyed). When given several treatment options, 74% of caregivers would have preferred to apply a nonsteroidal treatment as early as possible either to prevent a flare occurring or to prevent flares from getting worse.[96] [EL = 3]

A case series of 51 children with atopic eczema looked at the effects of parental education and demonstration of topical therapies by specialist dermatology nurses on therapy utilisation and severity of atopic eczema in children.[504] The study showed that after parental education there was an increase in the total quantity of emollient used (increase from a mean of 150 g weekly to 581 g weekly) and an increase in the number of children who used wet wraps (increase from 7.8% to 33%), suggesting better adherence to recommended treatment (the interval between the intervention and follow up varied, and the average interval or range was not reported).[504] [EL = 3]

The study in Japan explored the relationship between psychosocial factors and adherence to mite avoidance measures (such as removal of carpets, cleaning rooms daily and using anti-mite bedding) and skincare treatment by the mothers of children with atopic eczema (*n* = 205 mothers). Mite avoidance measures were more likely to be undertaken by families if the child also had asthma.[505] Mothers whose children used topical corticosteroids daily were more likely to follow skincare advice than those who did not use them daily. Mothers who showed high anxiety about using topical corticosteroids did not, however, report that they avoided their use. There was a tendency for the children who visited hospital more often to undertake more skincare treatment measures, like bathing every morning, using ointment every morning and using ointment more frequently during the day. Mothers' perception of the severity of atopic eczema was associated with both mite avoidance and skincare adherence.[505] [EL = 3]

Evidence statement for education and adherence to therapy

Education

Controlled trials that evaluated the effects of structured educational programmes for the treatment of atopic eczema in children were generally of poor quality. The available data showed improvements in a range of outcomes across the studies, including disease severity, quality of life, and self-management. [EL = 1−] There were no trials comparing different educational interventions and, therefore, the optimal educational package is unknown. [EL = 4]

Adherence to therapy

Surveys of parents and children with atopic eczema suggest that non-adherence to skincare treatment for atopic eczema by parents and children is influenced by fear of side effects of topical corticosteroids, stinging or itching caused by topical treatment, children being uncooperative with treatment, and treatment being too time-consuming. [EL = 3]

Cost-effectiveness

No cost-effectiveness studies were identified that addressed the role of education in improving adherence to treatment and health-related quality of life. There were very few empirical data on the effectiveness of educational interventions for children with atopic eczema. There was thus a lack of knowledge about what type of educational model (if any) would be optimal. The clinical evidence that does exist came from one high-quality German RCT.[498] However, no economic analysis was reported for that study.

A cost-effectiveness analysis was undertaken for the guideline using outcome data from the German RCT and data on the QALY value of mild, moderate and severe atopic eczema in children from the HTA for tacrolimus and pimecrolimus[291] (see Appendix D for details). Using 2005/06 UK cost data for NHS staff time and estimating the additional costs of training, the cost of implementing a similar programme in the NHS was calculated to be around £500 in staff time alone to run a series of six 2 hour education sessions. Additional overhead and variable costs would be incurred, but details of the other resources required to run the programme were not described in

the German RCT. The analysis undertaken for this guideline therefore focused on estimation of the maximum cost per child for an education programme to be cost-effective in the NHS (using the NICE threshold for cost-effectiveness of £20,000 per QALY).

The results of the analysis indicated that if an educational programme similar to that described in the German RCT could be provided in the NHS at less than about £800 per child, then it would be highly likely to be cost-effective. Sensitivity analysis was performed by varying costs and outcome values and changing some basic assumptions in the model), resulting in cost-effectiveness ratios that were favourable to educational interventions. Even though a programme such as that described in the German RCT would be unlikely to be implemented in the NHS in the near future, a less resource-intensive (and less-effective) programme that could be implemented in the NHS was likely to be cost-effective.

Early educational interventions similar to those run in German clinics for children with atopic eczema could be both effective and good value for money. Such programmes could, therefore, be a worthwhile area of focus for secondary care services aimed at children with atopic eczema.

From evidence to recommendations

The GDG believes that education plays a significant role in determining the effectiveness and success of the management of atopic eczema in children, and that the most important interventions are listening to the child and their parents/caregivers, providing verbal and written information, and providing practical demonstrations of topical therapies and dressings. [EL = 4] It is the GDG's view that the purpose of educating children and their parents/caregivers is to transfer knowledge and skills, thereby empowering children and parents/caregivers to perform effective self-management of the condition. As well as informing children with atopic eczema and their parents and carers about the quantities of topical therapies that should be used, it may be helpful to ask about the quantities that have been used recently.

It is the GDG's view that education leads to improved adherence to therapy for atopic eczema, and that direct involvement in treatment choices leads to improved adherence to skincare treatment regimens. Early educational interventions in secondary care have the potential to be highly cost-effective and therefore pilot studies to evaluate the best way of running these programmes in the NHS should be viewed as a priority for research.

The GDG believes that adherence to therapy can be improved when the cultural bathing practices of the child are taken into consideration. For example, some ethnic groups use a modified shower approach to bathing rather than immersion in a bath so information about emollient use should be adapted to suit their needs. In some cultural groups it is common practice to oil the skin and healthcare professionals should be aware that the oils used may irritate the skin.

The GDG's clinical experience is that black and Asian ethnic groups show a tendency for particularly dry skin, although the GDG found no evidence to support this.

Recommendations for education and adherence to therapy

Healthcare professionals should spend time educating children with atopic eczema and their parents or carers about atopic eczema and its treatment. They should provide information in verbal and written forms, with practical demonstrations, and should cover:

- how much of the treatments to use
- how often to apply treatments
- when and how to step treatment up or down
- how to treat infected atopic eczema.

This should be reinforced at every consultation, addressing factors that affect adherence.

When discussing treatment options with children with atopic eczema and their parents and carers, healthcare professionals should tailor the information they provide to suit the child's cultural practices relating to skin care (including oiling the skin) and the way they bathe.

Healthcare professionals should inform children with atopic eczema and their parents or carers that atopic eczema may temporarily cause the skin to become lighter or darker.

Research recommendations for education and adherence to therapy

How effective and cost-effective are different models of educational programmes in the early management of atopic eczema in children, in terms of improving adherence to therapy and patient outcomes such as disease severity and quality of life?

Why this is important

Atopic eczema is a common childhood disease affecting one in five children in the UK. Effective therapy improves quality of life for children with atopic eczema and their parents and carers, and can be provided for over 80% of children with atopic eczema in a primary care setting. It is known that a lack of education about therapy leads to poor adherence, and consequently to treatment failure.

9 Monitoring growth

Body length, weight and head circumference are recorded at birth, and growth is measured routinely in infancy using these three parameters. Centile charts based on the general UK population are used to determine whether growth measurements fall within 'normal' limits. Routine monitoring of growth in children is not continued beyond the first few years of life unless there are specific concerns about growth or if a child requires specialist care in a paediatric unit for any reason. The growth of children from ethnic groups other than white may not conform to UK charts, although in practice UK charts are used for all ethnic groups.

It was first noted in the 1940s that short stature may be associated with allergic diseases.[506] Major research in this area began in the late 1960s with the introduction of corticosteroid treatments. Initially research focused on the effect of asthma on growth, and only later was it realised that atopic eczema was also associated with poor growth in around 10% of severely affected children. The causes of growth disturbance are complicated and multifactorial. It is been suggested that the presence of severe atopic eczema, coexistence of asthma, use of corticosteroid therapy, chronic stress and sleep disturbance (with possible alteration of growth hormone cycle), poor or restricted dietary intake and poor absorption may affect growth in children with atopic eczema.[507] The potential adverse effects of topical corticosteroids during growth spurts is also a question of major concern amongst healthcare professionals, but there are no data to confirm or refute this. [EL = 4] In this chapter evidence relating to growth disturbance in children with atopic eczema is considered.

Studies considered in this chapter

Controlled observational studies that compared growth in children with atopic eczema with growth in children without the condition were considered in this section, as were studies that investigated whether certain factors were associated with growth disturbance in children with atopic eczema. Nine studies investigated the effect of atopic eczema on growth and 13 considered the effects of various parameters on growth (corticosteroid treatment (n = 8), gastrointestinal disorders (n = 1) and dietary factors (n = 4)). No studies were identified in relation to chronic stress or sleep disturbance and growth hormone production.

Overview of available evidence

Measurement of growth in children with atopic eczema
Of the nine studies that measured growth in children with atopic eczema, one was a controlled trial with longitudinal follow-up,[508] three were cross-sectional studies without any longitudinal follow-up (where growth in children with atopic eczema was compared with growth in a control group or with average values),[509-511] and five were case series.[512-516]

Controlled study with longitudinal follow-up:
Seventy-seven children with atopic eczema (mean age 4.8 years, range 2.0–10.5 years) who were referred to a hospital unit due to the severity of their condition were compared with 71 children acting as controls.[508] [EL = 2−] Data concerning the percentage of skin affected and severity of the condition, potency of topical corticosteroids and asthma scores were collected from the children with atopic eczema. Growth measurements (height and height velocity standard deviation scores (SDSs), weight, body mass index (BMI) SD values, triceps and subscapular skinfold and bone age (TW2 method comparing bones in an X-ray of the fingers, hand and wrist with the bones of a standard atlas)) were obtained for both groups in years 1 and 2 of the study. Children with severe atopic eczema had normal growth parameters at the start of the study (there were no significant differences in height or height velocity SDSs compared with controls at the start of the study). However, the linear growth of children with atopic eczema was increasingly affected as they approached puberty. Height and height velocity SDS slowed down with age in the children with

atopic eczema (r = −0.37 and r = −0.31, respectively), and mean delays in bone age of 0.22 years at year 1 and 0.41 years at year 2 were reported. These delays were positively correlated with age (r = 0.39) and duration of atopic eczema (r = 0.39) and negatively correlated with height and height velocity SDS (r = −0.5 and r = −0.38, respectively). Linear growth was not affected by the extent of atopic eczema, use of topical corticosteroids or coexistence of asthma.

Cross-sectional studies without any longitudinal follow-up:
In the first study, children with atopic eczema severe enough to be referred to a hospital consultant underwent growth measurements, which were compared with the general population using standard growth charts (n = 89, age range 1.3–16.95 years).[510] [EL = 3] Ten percent of the children (of whom seven were boys and two were girls) had a standing height below the third centile. Both boys and girls had statistically significant reduced sitting height (P < 0.001) and the difference between sitting height and subischial leg length was disproportionately smaller than normal values (mean value 0.55 SD for boys and 0.88 SD for girls). The mean head circumference was greater than the mean for the general population for both boys (P < 0.01) and girls (P < 0.02). Skeletal maturity was delayed as measured by the TW2RUS method (a modification of the TWR method) in both girls (P < 0.001) and boys (P < 0.05). Weight and skinfold tests were comparable to the general population. Disease severity, topical corticosteroid use for atopic eczema and asthma scores appeared to be associated with decreasing centile height.[510]

In the second study, the parents of 128 children with atopic eczema (age range 1.2–16.2 years) who had been referred to a hospital consultant (no details of severity reported) and 117 healthy children (age range 1.1–16.5 years) were asked to respond to a postal questionnaire regarding demographic and growth data.[509] [EL = 2−] There were no significant differences in demographic characteristics such as age, parental employment and parental height between the groups. The mean SDS of the children with atopic eczema was significantly lower than that for the controls, even after adjusting for parental height (−0.4505 with standard error (SE) 0.119 versus −0.0595 with SE 0.097, P < 0.005). In 14 (11%) of the children with atopic eczema, the score was more than two SDs below the mean; 12 of these children also had asthma. The height SD values of the 57% of children with atopic eczema who reported no asthma, no antihistamine use and no systemic corticosteroid use remained significantly lower than the controls after adjusting for age and parental height (P < 0.01).[509]

In the third study, growth parameters of 35 adults (age range 18–50 years) with childhood atopic eczema that had persisted into adulthood were compared with 35 controls (age range 18–46 years) with adult-onset contact dermatitis or adult-onset psoriasis and no atopic disease.[511] [EL = 3] There were no significant differences between the atopic eczema group and the control group in terms of standing height, mid-parental height, sitting height or subischial leg length (all measured as SDSs), or BMI. Further analysis looking at the influence of severity of atopic eczema (surface area affected), use of topical corticosteroids and presence of asthma showed no differences between the two groups.

Case series:
A case series recorded height SD, maximum surface area of skin ever affected, topical and systemic corticosteroid use, presence of asthma and exclusion diets in children with atopic eczema during consultation in a hospital setting (n = 68 children, age range 2.3–11.9 years).[512] [EL = 3] Bone age was measured in children older than 6 years. The median surface area of skin affected by atopic eczema was 30%. Height SD scores were significantly correlated with the surface area of skin affected by atopic eczema (r_s = 0.42, P = 0.03). These results should be interpreted with caution because of the difficulty in making an accurate assessment of the percentage of skin affected by atopic eczema. The mean height of the 41 children with 50% or less skin area affected was not significantly different from the expected value calculated from parental height (mean SDS −0.11). The mean height of the children with more than 50% of skin area affected was significantly shorter than the expected value calculated from parental height (SDS −0.83, P < 0.001). Regression analysis suggested that parental height was the most important factor influencing children's height, followed by severity of atopic eczema. Dietary factors and topical corticosteroid use had a weaker relationship with children's height. Presence of asthma and duration of atopic eczema were not related to children's height.[512]

In the second case series, growth was measured by skinfold thickness (triceps and subscapular), BMI, relative body weight and height SDS in children with atopic disease (78% with atopic eczema (no severity details reported) of whom 13% also had asthma; *n* = 92, age range 0.51–10.5 years).[513] [EL = 3] The children's data were analysed separately for children under 3 years and those aged at least 3 years (there was no control group). In children under 3 years, 11/36 children in terms of weight, 14/36 in terms of height and 7/36 in terms of weight-for-height were above the 90th centile, although body weight and BMI were within normal limits. In children aged at least 3 years, weight-for-height was high (20/56 were above the 90th centile) and the BMI and triceps and subscapular skinfold thickness were above the 90th centile in 16/56, 20/56 and 17/56 of children, respectively. Seventeen out of 56 children aged at least 3 years also exceeded the 120% relative weight (that is, they were obese).

In the third case series, growth parameters were measured for 70 male and 40 female patients who had developed atopic eczema in early childhood (median age of onset 0.7 years, range 0.01–5.0 years) which persisted into young adulthood.[514] [EL = 3] Of these, 84% also had a history of asthma, of which 92% of cases were mild. Patients recruited to the study were aged 16 years or over and had at least 4 growth measurements (height and weight) recorded over a minimum of 1 year during childhood. Male (female) patients were shorter than would be expected for the general population throughout childhood, with a height SDS of −0.9 (−0.6) at 12 years (7.9 years), but they showed a partial catch-up afterwards. Weight showed a similar trend. The BMI SDS line for males (females) was above zero (that is, above average for the general population) throughout childhood, but fell to −0.07 (−0.3) by 13.8 years (9.1 years). The age at adiposity rebound (the second rise in BMI during childhood) was later than for the general population for both males and females (6.2 years versus 5.4 years and 6.2 years versus 5.3 years, respectively). Normally children with a higher BMI tend to reach puberty earlier than other children. In these patients with atopic eczema, peak height velocity was attained later than the 1990 UK population (males 16.0 years versus 13.5 years, $P = 0.0002$; females 13.4 years versus 11.0 years, $P = 0.008$). In addition, males had a greater mean gain in height during late adolescence (12.2 cm versus 8.8 cm, $P = 0.03$) and were shorter as young adults (170.9 cm versus 177.6 cm, $P = 0.0005$).

In the fourth case series, historical and current growth data were obtained through structured interviews (conducted either at the GP surgery or at home) with 256 7-year-old children.[515] [EL = 3] The questionnaire comprised three parts relating to demographics, history of illness including wheezing and atopic eczema (using the ISAAC criteria), and growth data obtained from the Personal Child Record Book and measurements made at the time of the study by the health visitor. Atopic eczema (no details of severity were reported) in children at age 7 years did not appear to be related to any growth measurements at birth or during infancy. In the general population the majority of childhood atopic eczema cases are mild and therefore growth disturbance would be expected only in severe cases.

The fifth case series investigated growth measures from a birth cohort of New Zealand children.[516] [EL = 3] From an original cohort of 1265 children there were complete data for 70% on patterns of atopic disease up to the age of 16 years. Data on perinatal measures and incidence of atopic disease were ascertained by interview, hospital, GP and parental records using percentage figures (rates) of diagnosis and records from medical consultations. There was no association between the incidence of atopic eczema and birth weight ($P < 0.80$), gestational weight ($P < 0.4$), head circumference ($P < 0.80$) or length at birth ($P < 0.60$).[516]

Effects of corticosteroids on growth

Of the eight studies that measured the effects of corticosteroids on growth or biochemical markers of growth disturbance, six were case series[331,517-521] and two were case reports.[522,523] Further studies that evaluated effects of topical corticosteroids on adrenal function are described in Section 7.2.

Case series:

Two of the case series investigated adrenocortical responsiveness in children with atopic eczema following topical corticosteroid treatments.[517,518] The first study investigated 20 children (age range 5–12 years) with 'stable' atopic eczema who were treated with hydrocortisone butyrate 1% cream three times a day for up to 4 weeks. A tetracosactride (synthetic adrenocorticotrophic hormone)

was used to challenge the responsiveness of the adrenal gland. All 20 children improved in terms of their atopic eczema as measured by the Physician's Global Assessment scale, a pruritus scale and percentage body surface affected. No children were found to exhibit adrenal suppression at the end of the study (mean post-stimulation cortisol concentration level 27.8 ± 4.5 µg/dl). The second study included 14 children (age range 3 months to 14.4 years) who had been admitted to hospital owing to exacerbation of their atopic eczema. They were treated with hydrocortisone butyrate 1% cream and serum cortisol assays were used to measure percutaneous absorption of hydrocortisone over a 24 hour period. Ten of the children underwent a tetracosactride stimulation test and their cortisol responses were measured at 2 hours. Three of the ten children had suppressed adrenocortical function and this was associated with high serum cortisol levels post application of hydrocortisone.

Three of the case series were small and involved short-term treatment (2–3 weeks) with topical corticosteroids (beclometasone dipropionate 10% or 25%, or budesonide 0.025% cream). The outcome measures were of limited clinical value: lower leg length and biochemical measures of growth and bone turnover and showed no clinically significant effects of the treatment.

The fifth case series was of 6 months' duration and investigated the use of treatment with oral beclometasone dipropionate (n = 10, mean dose 1800 µg/day). Median height SDS was reduced, with 70% showing some sign of growth impairment. Serum cortisol levels were reported to be reduced, but the reductions were not statistically significant. [EL = 3]

Case reports:
Two case reports reported severe adverse effects of topical corticosteroids on the growth of children with atopic eczema since the introduction of these treatments in the 1960s. However, the US Food and Drug Administration (FDA) adverse event reporting system contains 22 cases of immunosuppression among patients aged 6 weeks to 15 years using topical corticosteroids (no further details available).

Of the published case reports, one described a 5-year-old boy with atopic eczema treated with betamethasone valerate 0.1% and clobetasol propionate 0.05% for the previous 6 months. The boy was small for his age and had suppressed adrenocortical function. The second case report described a 13-year-old boy with short stature who had been treated for 18 months with betamethasone 2% ointment. In both cases, treatment was reviewed and changed. No follow-up was reported for the first case, but in the second case improved growth was reported at 6 and 12 months.

Effects of gastrointestinal disorders on growth
In a cross-sectional study, 65 children with atopic eczema were compared with 65 children who were unaffected by the condition (age range 6 months to 14 years for both groups) by investigating the incidence of gastrointestinal symptoms.[524] [EL = 2−] Questionnaire data showed that gastrointestinal symptoms including prevalence of diarrhoea ($P < 0.001$), vomiting ($P < 0.01$) and regurgitation ($P < 0.001$) were significantly more common in children with atopic eczema than in the control group. There was no significant difference in age, height, weight and eleventh-rib circumference between the atopic eczema and control groups.

Effects of diet on growth
Of the four studies that measured the effects of diet on growth, two were controlled studies with longitudinal follow-up[525,526] and two were uncontrolled longitudinal studies.[527,528]

Controlled studies with longitudinal follow-up:
The growth of 55 infants with atopic eczema (36 breastfed and 19 not breastfed) was followed during the first 12 months of life and compared with growth in 114 healthy infants (58 breastfed and 56 not breastfed) using standardised growth indices.[525] [EL = 2−] No difference was found between the groups at birth (e.g. gestational age, birth weight and height). In infants with atopic eczema, weight-for-age and length-for-age normal (z) scores (anthropometric indices representing the distance in SD units from the Centers for Disease Control and Prevention–World Health Organization normative reference data adjusted for age) decreased with age and were significantly lower compared with healthy infants from the second month of age onwards. The difference of mean z scores between atopic eczema and healthy infants at 12 months of age was

−0.69 (95% CI −1.00 to −0.38) for weight-for-age and −0.67 (95% CI −0.98 to −0.36) for length-for-age. The growth of infants with atopic eczema was not influenced by the type of early feeding. However, in the 6–12 month period, the delay in growth was more pronounced in infants with more severe atopic eczema ($P < 0.05$).

A controlled study of 100 infants (age range 1–17 months) with atopic eczema examined the effect of a cow's milk elimination diet (extensively hydrolysed casein, whey or soya formula) on growth.[526] [EL = 2−] Children in the control group ($n = 60$) were recruited from a baby clinic. Clinical control of atopic eczema symptoms was achieved in all infants. The mean length SDS score and weight-for-length index of the infants with atopic eczema decreased compared with those of the healthy, age-matched infants ($P < 0.0001$ and $P = 0.03$, respectively). No catch up was seen at 24 months. Low serum albumin was present in 6% of the children with atopic eczema, 24% had an abnormal urea concentration, and 8% had a low serum phospholipid docosahexaenoic acid concentration. Growth was delayed more in a subgroup of children with early onset of atopic eczema than in those with later onset of symptoms ($F = 6.65$, $P < 0.0001$).

Uncontrolled studies with longitudinal follow-up:
A prospective study of infants from birth to 48 months ($n = 159$) with a family history of allergic disease and whose mothers had previously participated in a prenatal probiotic study was carried out.[527] [EL = 3] Dietary supplementation with probiotics (*Lactobacillus rhamnosus* strain GG; ATCC 53103) was administered to the infants postnatally for 6 months. Atopic eczema was diagnosed in 36% of the infants (39/107) at 48 months. Perinatal administration of probiotics did not influence the height (mean difference 0.04 SDS, 95% CI −0.33 to 0.40, $P = 0.852$) or weight-for-height (mean difference −3.35%, 95% CI −7.07% to 0.37%, $P = 0.077$) of the infants at 48 months with and without perinatal administration of probiotics. Up to 48 months, atopic eczema did not affect height (mean difference −0.05 SDS, 95% CI −0.42 to 0.33, $P = 0.815$), but mean weight-for-height in infants with atopic eczema was −5.1% lower (95% CI −8.9% to −1.2%) than in children without atopic eczema ($P = 0.010$).

An uncontrolled longitudinal study evaluated the effects of extensively hydrolysed milk formula on the growth of 45 infants and toddlers for 1 year (age range 1.0–27 months old) with a history of cow's milk allergy.[528] [EL = 3] Similar percentiles of the children's weight (95% CI −3.1 to −2.3) and height (95% CI −5.2 to 8.1) were observed at the beginning of the study and 1 year later. Multivariate analysis showed that sex, breastfeeding, early bottle feeding, ingestion of adapted or special milk formulas, atopic eczema, and bronchitis were not correlated with the children's weight and height at diagnosis of the allergy or at 1 year of follow-up ($P > 0.10$). Atopic eczema was reported in 18 of the children at the beginning of the study and 13 at the end. Weights (95% CI −0.6 to 2.6 kg) and heights (95% CI −1.5 to 0.5 cm) were not different between toddlers who had atopic eczema or bronchitis during the study period and those who did not.

Management of growth disturbance
No studies that focused on the management of growth in children with atopic eczema as a primary outcome were identified, although many of the studies described above concluded that their results should impact on clinical practice.

Evidence statement for monitoring growth

Few studies of appropriate design considered whether children with atopic eczema experienced growth disturbance and whether there was any effect on their eventual height as adults. [EL = 3] There was some evidence to show that a small proportion of children, usually with more severe atopic eczema (> 50% surface area affected), may be shorter than predicted compared with their peers, but no evidence was found to suggest that this effect persisted into adult life. [EL = 3] There was some evidence to suggest that there was no difference in mean height between adults with lifelong atopic eczema and their peers, but few studies have had adequate duration of follow-up. [EL = 3] Evidence for a causal relationship between treatment with topical corticosteroids (or coexistence of asthma) and observed effects on growth was inconclusive. [EL = 3]

Adrenocortical suppression has been demonstrated following the short-term application of mild potency topical corticosteroid to large areas of inflamed skin and following the prolonged application of more potent topical corticosteroids. [EL = 3] However, the clinical relevance of

adrenocortical suppression following topical corticosteroid use has not been fully explored (see Section 7.2). Adrenocortical suppression has been shown to occur following the application of wet wraps over topical corticosteroid therapy (see Section 7.4).

One study suggested that there was a delay in puberty in children with atopic eczema, but in general there was no evidence to support the hypothesis that topical corticosteroids affect growth, except in isolated cases where they were used outside their licensed indications or in greater quantities than would normally be recommended.

There were no data to suggest that specific diets influenced growth of children with atopic eczema, although again data were lacking. There was evidence from one study to suggest that growth disturbance occurred in children with cow's milk allergy treated with an elimination diet. [EL = 3] One survey suggested that infants with atopic eczema experienced more gastrointestinal symptoms than infants without the condition. [EL = 3]

Cost-effectiveness

No published evidence relating to the cost-effectiveness of measuring growth in children with atopic eczema was identified. The GDG believes that it is cost-effective to monitor growth in children with atopic eczema that requires ongoing treatment because early identification of failure to thrive may reduce later morbidity and associated downstream healthcare costs.

From evidence to recommendations

Although there was some research on the growth of children with atopic eczema and the factors that may influence it, it was difficult to extrapolate the data to clinical practice. The studies from which the data arise were short term and some involved less commonly used and less clinically relevant parameters such as lower leg growth and bone age. More research is needed and future studies should have a more pragmatic approach to measuring growth. There was a lack of data on the effect of chronic stress and sleep disturbance on growth of children with atopic eczema, which also needs addressing by future research.

The GDG believes that it is cost-effective to monitor growth in children with atopic eczema that requires ongoing treatment. The aim of monitoring should be to identify failure to thrive (which may reflect the severity of the atopic eczema), and therefore inform treatment decisions, including referral. Failure to thrive in atopic eczema often indicates another problem (such as nutritional deficiency or food allergy). Early identification of failure to thrive (discrepancy between height and weight, or stunted growth) may prevent later morbidity. The GDG adopted the advice given in the UK growth charts regarding what falls outside normal growth limits. Taking parental heights into consideration, children usually grow along their projected growth centile and reach puberty within a demarcated age range; deviation from this (falling across 10 centiles over a 1–2 year period, or delay in the onset of puberty; 13.5 years for girls and 14 years for boys) is an indication for referral.

There were no specific recommendations for monitoring growth but recommendations on referral in relation to growth can be found in Chapter 10.

Research recommendations for monitoring growth

Which factors contribute to growth delay in children with severe atopic eczema, how should they be managed and does this impact on their expected final adult height?

Why this is important
It is known that 10% of children with severe atopic eczema have a corrected height below that expected from centile charts based on the general UK after taking into account their parental heights. However, the causes for this are not fully understood. This study is necessary to understand the causes of growth delay in order to provide the correct management to maximise 'catch-up' growth and achieve an adult height appropriate for that child. The study should consider the effects of chronic stress and sleep disturbance on the growth of children with atopic eczema.

What is the impact of food allergy on growth in infants with atopic eczema and how should it be managed?

Why this is important
Food allergy should be suspected in infants with atopic eczema and failure to thrive. The percentage of children with eczema who have poor growth because of food allergy is not currently known. Research is required to determine this in order to plan the most effective and cost-effective feeding regimens to manage these children.

10 Indications for referral

Since atopic eczema follows a remitting and relapsing course, referral may be needed at the time of diagnosis or at any subsequent clinical assessment. There is a lack of data regarding patterns of referral for children with atopic eczema across the UK. The 1991 Royal College of General Practitioners (RCGP) morbidity survey reported general practice consultation rates for atopic eczema but not referral rates.[529] A survey of 1- to 5-year-old children in Nottingham found that 6% of children with atopic eczema were referred for specialist advice in a 12 month period. The referral rate was higher in those with atopic eczema classified as severe (43%) rather than moderate (15%) or mild (3%). The exact reasons for referral were not reported.[123]

Studies considered in this chapter

No clinical or cost-effectiveness evidence was identified in relation to referral and treatment outcomes in children with atopic eczema. In the absence of such evidence, the GDG members drew on referral advice in other guidance,[11,530] and on their collective experience to determine indications for referral for children with atopic eczema.

Evidence statement for indications for referral

No clinical or cost-effectiveness evidence was identified in relation to referral and treatment outcomes in children with atopic eczema.

From evidence to recommendations

The GDG's recommendations for referral are designed to ensure that children who require referral are referred more promptly and that inappropriate referral is minimised. Also, the recommendations distinguish between immediate (same-day) referral, urgent referral (within 2 weeks) and non-urgent (routine) referral. It is the GDG's view that this will lead to more cost-effective referral practice. Furthermore, the GDG believes that its referral recommendations will not have significant resource impacts for the NHS since the majority of its recommendations reflect existing clinical guidance and practice.

The GDG drew on referral advice given in other guidance (including NICE referral advice[11]), and on the members' consensus to determine indications for referral for children with atopic eczema. The main clinical situations that the GDG used to identify indications for referral for specialist advice are where:

- the diagnosis is uncertain
- optimal topical treatment has not controlled the condition (as indicated by frequency of flares and/or potency of treatment) or the next step of treatment requires specialist knowledge (for example, bandaging)
- other complications that warrant further investigation and/or management are suspected (such as food allergy, contact dermatitis or bacterially infected atopic eczema that has failed to respond to treatment).

The GDG believes that referral in these circumstances will be cost-effective, as it should increase appropriate treatment for those who require it and decrease inappropriate/unnecessary treatment for those who do not.

Immediate (same-day) referral is needed when the indication is potentially life-threatening. Urgent referral (within 2 weeks) is recommended when all initial options have been exhausted (that is, they are ineffective or have caused unacceptable adverse effects) and the condition is affecting quality of life and/or schooling. Infected atopic eczema needs urgent referral because of the risk of complications from the infection.

The type of specialist advice required for each indication was specified when developing the recommendations, but because of geographical variations in service configuration it was not possible to state to which service children should be referred. For example, referral for specialist dermatological advice could mean referral to a dermatology specialist nurse, a GP with a special interest in dermatology, or a dermatologist, depending on local circumstances.

Recommendations for indications for referral

Immediate (same-day) referral for specialist dermatological advice is recommended if eczema herpeticum is suspected.

Urgent (within 2 weeks) referral for specialist dermatological advice is recommended for children with atopic eczema if:

- the atopic eczema is severe and has not responded to optimum topical therapy after 1 week
- treatment of bacterially infected atopic eczema has failed.

Referral for specialist dermatological advice is recommended for children with atopic eczema if:

- the diagnosis is, or has become, uncertain
- management has not controlled the atopic eczema satisfactorily based on a subjective assessment by the child, parent or carer (for example, the child is having 1–2 weeks of flares per month or is reacting adversely to many emollients)
- atopic eczema on the face has not responded to appropriate treatment
- the child or parent/carer may benefit from specialist advice on treatment application (for example, bandaging techniques)
- contact allergic dermatitis is suspected (for example, persistent atopic eczema or facial, eyelid or hand atopic eczema)
- the atopic eczema is giving rise to significant social or psychological problems for the child or parent/carer (for example, sleep disturbance, poor school attendance)
- atopic eczema is associated with severe and recurrent infections, especially deep abscesses or pneumonia.

Children with atopic eczema that has responded to optimum management but for whom the impact of the atopic eczema on quality of life and psychosocial wellbeing has not improved should be referred for psychological advice.

Children with moderate or severe atopic eczema and suspected food allergy should be referred for specialist investigation and management of the atopic eczema and allergy.

Children with atopic eczema who fail to grow at the expected growth trajectory, as reflected by UK growth charts, should be referred for specialist advice relating to growth.

There were no research recommendations relating to indications for referral.

Appendix A

Declarations of interest

This appendix includes all interests declared on or before 5 November 2007.

A.1 Guideline Development Group members

Denise Carr

No interests declared

Christine Clark

Personal pecuniary interests
Specific: Consultancy and medical writing for ARX, Beiersdorf UK, Carmel Pharma, LEO Pharma, Royal Pharmaceutical Society of Great Britain and Schering Plough UK; shares in GlaxoSmithKline and Shire

Non-current interests
Previous: Consultancy and medical writing for Crookes Healthcare Ltd

Planned: Consultancy and medical writing for York Pharma

Michael Cork

Personal pecuniary interests
Specific: Consultancy for Novartis (pimecrolimus) and shares in York Pharma (developing treatments for atopic eczema); funding from Galderma Canada to attend dermatology update meeting

Non-specific: Shares in Strakan Pharmaceuticals (no treatments for atopic eczema or related diseases)

Non-personal pecuniary interests
Specific: Research funding from Novartis and York Pharma

Non-specific: Support for attending dermatology meetings and conferences from LEO Pharma and Novartis

Non-current interests
Previous: Consultancy for Boots group (emollients and unlicensed cosmetic products) and GlaxoSmithKline (topical corticosteroids)

Helen Cox

No interests declared

Elizabeth Gilmour

No interests declared

Wendy Lancaster

Sandra Lawton

Personal pecuniary interests
Specific: Expenses and/or lecture fees from Crawfords Pharmaceuticals and LEO Pharma

Personal non-pecuniary interests
Professional membership of the Royal College of Nursing, British Dermatological Nursing group and special interest groups for primary care, paediatrics and non-medical prescribing, and Dermatology Nursing Association USA; advisory group member for All-Party Parliamentary Group on Skin; member of National Eczema Society

Non-personal pecuniary interests
Specific: Sponsorship for local educational conferences

Non-current interests
Planned: Invited to speak at Primary Care Dermatology Society meeting sponsored by LEO Pharma and invited to speak by Reckitt Benckiser

Sue Lewis-Jones

Personal pecuniary interests
Specific: Advisor to Astellas, LEO Pharma and Novartis; reviewed paediatric dermatology treatments for the British National Formulary; lecture fees from Primary Care Dermatology Society

Personal non-pecuniary interests
Trustee of British Skin Foundation

Non-personal pecuniary interests
Specific: Co-holder of copyright for quality of life questionnaires (CDLQI, DFI and IDQoL; royalties paid to departmental research funds); research funding from Anonymous Trust 2007 Award and British Skin Foundation

Non-current interests
Previous: Advisor to LEO Pharma and Novartis; conference expenses and/or lecture fees from Barrier Therapeutics, LEO Pharma, Novartis, Schering-Plough and Wyeth; sponsorship for dermatology training courses from Crookes Healthcare Ltd, Dermol, Fujisawa, Galderma Typharm, LEO Pharma, Novartis, Neutrogena and Stiefel Laboratories; clinic equipment (digital camera) from LEO Pharma; research funding from EastRen Research, Glaxo, National Eczema Society, Novartis, Sandoz, SR Pharma, Tayside University Hospitals Trust and Welsh Committee for Research and Development

Planned: Invited to chair meeting organised by York Pharma; conference expenses and/or lecture fees from LEO Pharma; invited to chair Primary Care Dermatology Society meeting sponsored by LEO Pharma

Sarah Purdy

Personal non-pecuniary interests
Faculty Board Member, Royal College of General Practitioners, Non-Executive Member of Prescription Pricing Authority, Honorary Clinical Senior Lecturer, University of Newcastle

Personal family interests
Spouse is Director and Board Member of United Bristol Healthcare NHS Trust

Amanda Roberts

Personal pecuniary interests
Non-specific: Member of the East Midlands Regional Funding Committee for the Research for Patient Benefit Programme of the National Institute for Health Research; shares in Boots group

Personal non-pecuniary interests
Involved in running the Nottingham Support Group for Carers of Children with Eczema

Non-personal pecuniary interests
Specific: the Nottingham Support Group for Carers of Children with Eczema has been invited to participate in research for Novartis

Jean Robinson

Personal pecuniary interests
Specific: Shares in Reckitt Benckiser

Non-personal pecuniary interests
Specific: Development of an educational tool for atopic eczema funded by LEO Pharma

Sue Ward

Non-personal pecuniary interests
Specific: The National Eczema Society will receive funding for preparing an article on trigger factors in eczema

Non-specific: The National Eczema Society receives funding from several pharmaceutical companies

A.2 NCC-WCH staff and contractors

Paula Broughton-Palmer

No interests declared

Hannah-Rose Douglas

No interests declared

Alyson Huntley

Personal pecuniary interests
Specific: Writing article on complementary therapies for eczema in adults for MIMS Dermatology

Moira Mugglestone

No interests declared

Anne Marie O'Connell

No interests declared

Julia Saperia

No interests declared

A.3 External advisers

Carolyn Charman

Personal non-pecuniary interests
Research interest in scoring and measurement of severity of atopic eczema

Non-current interests
Previous: Sponsorship for educational meetings from LEO Pharma and Novartis and guest speaker at press workshop sponsored by Novartis; holder of a Health Service Research Fellowship funded by the NHS Research and Development Programme (measuring atopic eczema severity: improving outcomes measures for research and clinical practice)

Stephen Greene

Personal pecuniary interests
Specific: Funding for paediatrics from NHS Scotland, for diabetes from the University of Dundee, and for chronic health disorders in children from the Royal College of Paediatrics and Child Health

C Anthony Hart

Personal pecuniary interests
Non-specific: Shares in AstraZeneca

Non-personal pecuniary interests
Non-specific: Lecture fees from Chiron for non-promotional meetings

Penny Titman

No interests declared

Hywel Williams

Personal non-pecuniary interests
Research interest in causes and management of atopic eczema in children

Non-personal pecuniary interests
Specific: research funding from the NHS, including the NHS Research and Development Programme

Appendix B

Clinical questions

Diagnostic criteria and classification of severity

1. What criteria should be used to diagnose atopic eczema in children and how do they vary between ethnic groups?
2. What measures should be used to classify the severity of atopic eczema in children in the setting of clinical management?

Management during and between flare-ups

3. What are the potential triggering factors for atopic eczema in children (including environmental irritants and allergens, dietary and psychological factors)?
4. How should triggering factors for atopic eczema in children be identified and managed?
5. What clinical tests should be used to identify relevant allergens and which children with atopic eczema would benefit from their use?
6. How should food allergies in children with atopic eczema be identified and managed?
7. How should flare-ups of atopic eczema in children be identified and managed?
8. How should atopic eczema in children be managed and monitored between flare-ups (maintenance therapy)?
9. What types of emollients are available for atopic eczema in children, how effective are they, what quantities should be used, and how often should they be used?
10. How effective and safe are topical corticosteroids for atopic eczema in children, and when and how often should they be used?
11. What types of dry bandages and medicated dressings (including wet wrap therapies) are available for atopic eczema in children, how effective and safe are they (particularly when combined with topical corticosteroids), and when and how often should they be used?
12. What is the most effective and safe way of combining different forms of therapy (for example, emollients, topical corticosteroids, bandaging techniques and calcineurin inhibitors)?
13. How effective and safe are antihistamines in the management of atopic eczema in children of different ages?
14. How effective and safe are other antipruritic (anti-itching) agents for atopic eczema in children and when should they be used?
15. What are the indications and precautions for using topical calcineurin inhibitors (pimecrolimus and tacrolimus) for atopic eczema in children and how effective and safe are they?
16. What are the indications and precautions for using systemic immunosuppressants (such as ciclosporin and azathioprine) for atopic eczema in children, how effective and safe are they, and how should their use be monitored?
17. What are the indications and precautions for using phototherapy for atopic eczema in children, how effective and safe is it and what form of phototherapy and length of treatment should be offered?

Complementary therapies

18. How effective and safe is homeopathy for managing atopic eczema in children?
19. How effective and safe are Chinese, Western and other herbal medicines for managing atopic eczema in children?
20. How effective and safe are other complementary therapies (for example, hypnotherapy) for managing atopic eczema in children?

Medical complications

21. What types of clinically significant secondary infections occur in atopic eczema in children and how should they be identified?
22. Which antimicrobial agents (including antiseptics) are effective and appropriate for treating infected atopic eczema in children?
23. How should antiseptic and antimicrobial resistance be managed in children with infected atopic eczema and what measures can be taken to reduce the risk of resistance developing?
24. What factors are involved in growth disturbance in children with atopic eczema and how should they be managed?

Psychological and psychosocial effects

25. How can psychological and psychosocial effects in children with atopic eczema and their families/carers be identified in everyday clinical settings?
26. How effective are behavioural therapy techniques for children with atopic eczema and what other effective psychological interventions are available?
27. How should the impact of atopic eczema on families'/carers' quality of life be assessed, and how effective is it to use quality of life and other health-related scales in routine clinical management?
    [Note: The wording of this question did not explicitly include children with atopic eczema, although it was always the GDG's intention that the question would cover children as well as their families/carers.]

Referral for specialist dermatological care

28. What are the indications for referral for specialist paediatric dermatological advice?

Information, education and support

29. What are the epidemiological characteristics of atopic eczema in children (including prevalence, age of onset and resolution, frequency, location and extent of flare-ups, associations with asthma, hay fever and food allergies, and variations in different ethnic groups)?
30. What management strategies are appropriate for different ages and cultural groups?
31. What factors contribute to non-adherence to therapy and how can adherence be improved?
32. How effective are education programmes for children with atopic eczema and their families/carers?
33. What information and support should be offered to children with atopic eczema and their families/carers?

Appendix C

Diagnostic accuracy of clinical tests for identifying trigger factors

C.1 Studies considered for the section on identification of trigger factors

Studies evaluating the accuracy of challenge tests (skin tests (skin prick tests, atopy patch tests and skin application food tests (SAFTs)) and immunoglobulin E (IgE) tests) for the identification of trigger factors for atopic eczema were considered for this section. Tests are available to investigate responses to irritants, allergens, microbial agents and foods, but not for climatic, psychological or environmental factors.

The double-blind placebo-controlled food challenge (DBPCFC) is considered to be the gold standard for the diagnosis of food hypersensitivity.[160] This test has been used to detect immediate responses (within 2 hours of ingestion of a specific food allergen) and delayed responses (2–72 hours after ingestion of allergen). A 2004 position paper from the European Academy of Allergology and Clinical Immunology regarding standardisation of food challenges in people with immediate reactions to foods stated that the double-blind challenge was the method of choice for studying late reactions or chronic symptoms, such as atopic eczema.[160] The position paper also recommended that a negative double-blind challenge be followed by an open food challenge to avoid false negative results due to destruction of the allergens during preparation of the foods.

There is no gold standard for identifying inhalant allergens.

A number of tests have been used within the research context but are of no use in clinical practice and are therefore not considered in the guideline. These include basophil histamine release tests, lymphocyte proliferation tests, eosinophil markers such as eosinophil cationic protein and eosinophil peroxidise, and tests that detect immunoglobulin G (IgG) responses to foods (IgG responses to foods can be found in both allergic and non-allergic people thus their presence indicates exposure to food allergen rather than any hypersensitivity reaction to that food).

C.2 Overview of available evidence

Much of the evidence relating to testing for allergens reported the rate of positive test results only. Such studies were not useful for evaluating the diagnostic accuracy of particular tests. In this section the GDG only considered studies that presented sufficient data for sensitivity and specificity, or positive and negative predictive values, for the test under investigation relative to a gold standard. Note that some studies were described in more than one publication.

No studies evaluated the accuracy of any test for diagnosing inhalant allergens.

Identifying food allergy in children with atopic eczema using the double-blind placebo-controlled food challenge (DBPCFC) as the reference test

Nine studies reported the diagnostic accuracy of two or three tests (atopy patch test, skin prick test and/or IgE) relative to a DBPCFC test.[161-170,181] An additional study considered the diagnostic accuracy of a skin prick test and IgE levels, but because definitions of a positive test on food challenge and on IgE testing were not reported this study was not considered further.[542]

Diagnostic accuracy of the tests to up to six allergens was investigated across the studies. Six studies considered the accuracy of the tests to detect allergy to cow's milk, egg, wheat and soya,[163-170,181] one of which also tested for allergy to fish and peanuts.[167,168] The two other studies

[illegible]r to wheat.[162]

In most studies it was not made clear whether the challenge testing was undertaken blind to the results of the tests being evaluated. It was also not explicit whether the population evaluated had atopic eczema that was suspected to be worsened by food allergy – it was thus not clear whether the populations were representative of people with atopic eczema who might undergo such testing. Six of the studies were considered to be of poor quality because of uncertainty over blinding to the results of other tests, whether the population reflected that in which the test would be used or whether open food challenges were allowed. [EL = DS III] Three studies were considered to be of better quality because the food challenges were undertaken by people who were unaware of the results of the other tests and/or the population reflected that in which the test would be used.[162–164,166] [EL = DS II]

The age range of children in the studies varied, but in six studies this was within the range of 2 months to 12 years. In two studies children up to the age of 18 years were included and in one study children up to 14 years were studied. In six studies all the children studied had atopic eczema; in the remaining studies 89–92% of the study population had the condition. The total number of children evaluated was 1224, ranging from 25 to 437 in individual studies.

One study stated that the atopic eczema was stabilised before the tests were undertaken.[181] In six studies the suspected food allergen(s) was excluded from the diet for 5 days to 4 weeks before testing.[161–164,166,170,181] Four studies reported that other treatments were permitted during the studies. Emollients and topical corticosteroids[169] or topical corticosteroids alone[163,164,166,181] were allowed, but not for 48 hours prior to skin testing in one study.[163,164] All except one study[167] stated that antihistamines were discontinued at least 72 hours before testing.

Tests were generally conducted in the same way across the studies. However, there were differences in the foods used, for example fresh foods or commercially available powdered foods. The placebo used, stated in all except one study,[167] was an amino acid milk substitute or a casein hydrolysate.

For patch testing, samples were left under occlusion for 48 hours and the skin reaction analysed 15–30 minutes after removing the patch. In most cases the reaction was also recorded after 72 hours. Positive tests were defined as erythema usually with infiltration. For the skin prick test, a positive test was considered to be a wheal size of 3 mm or greater, or when the area that reacted was a certain size in relation to the histamine reaction (the positive control used). Specific IgE levels were measured using the Pharmacia CAP method, with a level above 0.35 ku/l indicating a positive test across all studies.

Six studies reported the accuracy of the individual tests for each food allergen separately.[161,162,165–168,170,181] The other two reported only the accuracy data for all allergens together.[163,164,169]

Three studies reported the diagnostic accuracy of the tests for identifying immediate reactions.[165,167,168,170] Three studies reported the accuracy of the tests in diagnosing delayed reactions.[163,165,169] In four other studies the type of reaction recorded was unclear, but it was assumed for the guideline that the results presented included any reaction (that is, immediate or delayed).[161,162,166,181]

The prevalence of food allergy across the studies (that is, the proportion of positive test results on DBPCFC) was 46–58% (median 54%). Five studies reported the proportion of positive placebo food challenges, which were zero in three studies, and 2.6% and 3.8% in the other two.[161–164,169,170] The proportion of immediate reactions were in the range 23–100% (median 49%), delayed reactions 0–77% (median 26%), and combined immediate and delayed reaction (reported in five studies) 0–45% (median 22%). All the delayed reactions manifested as atopic eczema.

Diagnostic accuracy of tests for identifying an immediate reaction

Three studies reported the diagnostic accuracy of one or more of the tests for detecting an immediate reaction to one or more allergens on DBPCFC.[165,167,168,170] The results are summarised in Table C.1.

Two studies reported accuracy data for an immediate reaction to four allergens together (that is, a positive reaction to any one allergen constituted a positive reaction, but it is not clear which allergen(s) caused the reaction).[163,164,169] The results are summarised in Table C.2.

Table C.1 Diagnostic accuracy of tests for detecting immediate reactions to specific foods using a DBPDFC as the reference test[a]

Allergen	Test	Results (%)			
		Sensitivity	Specificity	PPV	NPV
Cow's milk	Atopy patch test (one study[165])	26	96	88	56
	Skin prick test (three studies[165,167,168,170])	43, 78, 96	51, 69, 75	60, 66, 72	60, 75, 93
	Specific IgE[b] (two studies[165,167,168])	85, 100	30, 38	57, 59	71, 100
Egg	Atopy patch test (one study[165])	44	93	89	57
	Skin prick test (three studies[165,167,168,170])	25, 89, 98	53, 57, 100	73, 85, 100	36, 80, 90
	Specific IgE (two studies[165,167,168])	94, 98	36, 45	65, 84	83, 88
Wheat	Skin prick test (one study[167,168])	90	51	35	94
	Specific IgE (one study[167,168])	96	20	14	97
Soya	Skin prick test (one study[167,168])	76	47	35	84
	Specific IgE (one study[167,168])	94	25	21	95
Fish	Skin prick test (one study[167,168])	90	57	77	80
	Specific IgE (one study[167,168])	94	65	49	97
Peanut	Skin prick test (one study[167,168])	90	29	55	75
	Specific IgE (one study[167,168])	97	38	78	85

[a] Data are arranged in numerical order rather than in the study sequence.
[b] A positive test was indicated by an IgE level of more than 0.35 ku/l.

Table C.2 Diagnostic accuracy of tests for detecting immediate reactions to groups of foods using a DBPCFC as the reference test[a]

Allergen	Test	Results (%)			
		Sensitivity	Specificity	PPV	NPV
Cow's milk, egg, wheat, soya	Atopy patch test (two studies[163,164,169])	33, 67	38, 95	38, 81	67 (both studies)
	Skin prick test (one study[163,164])	95	70	69	95
	Specific IgE (two studies[163,164,169])	77, 95	29, 60	57, 62	59, 79

[a] Data are arranged in numerical order rather than in the study sequence.

Diagnostic accuracy of tests for identifying delayed reactions (atopic eczema)
One study reported accuracy data for the atopy patch test, skin prick test, and specific IgE levels for detecting delayed allergy to cow's milk and egg separately.[165] This study also considered the diagnostic accuracy for IgE if the threshold for a positive test was higher (17.5 ku/l rather than 0.35 ku/l). In both cases the sensitivity and NPV fell, and the specificity and PPV increased.[165] The results are shown in Table C.3.

Two studies considered the accuracy of atopy patch test and specific IgE to detect a delayed reaction (exacerbation to atopic eczema) to cow's milk, egg, wheat or soya.[163,164,169] The studies reported the accuracy for all allergens together.[163,164,169] The results are summarised in Table C.4.

Diagnostic accuracy of tests for identifying any reaction (immediate and/or delayed)
Five studies reported the diagnostic accuracy of one or more of the tests for detecting any response (immediate and/or delayed) to one or more allergens on DBPCFC.[161,162,165,166,181] The results are summarised in Table C.5.

Three studies reported accuracy data for any response to four allergens together.[163,164,166,169] The results are shown in Table C.6.

Table C.3 Diagnostic accuracy of tests for detecting delayed reactions to specific foods using a DBPCFC as the reference test

Allergen	Test	Results (%)			
		Sensitivity	Specificity	PPV	NPV
Cow's milk	Atopy patch test (one study[165])	78	96	93	86
	Skin prick test (one study[165])	78	69	64	82
	Specific IgE (one study[165])	83	38	48	77
Egg	Atopy patch test (one study[165])	80	93	89	87
	Skin prick test (one study[165])	90	57	60	89
	Specific IgE (one study[165])	100	38	53	100

Table C.4 Diagnostic accuracy of tests for detecting delayed reactions to groups of foods using a DBPCFC as the reference test[a]

Allergen	Test	Results (%)			
		Sensitivity	Specificity	PPV	NPV
Cow's milk, egg, wheat, soya	Atopy patch test (two studies[163,164,169])	67, 76	38, 95	24, 81	79, 93
	Skin prick test (one study[163,164])	58	70	41	81
	Specific IgE (two studies[163,164,169])	68, 71	29, 50	33, 37	72, 81

[a] Data are arranged in numerical order rather than in the study sequence.

Table C.5 Diagnostic accuracy of tests for detecting any reaction (immediate and/or delayed) to specific foods using a DBPCFC as the reference test[a]

Allergen	Test	Results (%)			
		Sensitivity	Specificity	PPV	NPV
Cow's milk	Atopy patch test (three studies[161,165,181])	31, 47, 61	81, 96, 95	95, 96[b]	51, 60[b]
	Skin prick test (three studies[161,165,181])	48, 78, 85	69, 86, 70	73, 81[b]	64, 83[b]
	Specific IgE (three studies[165,166,181])	84, 85, 87	38, 38, 49	61, 62, 70	59, 71, 79
Egg	Atopy patch test (two studies[165,181])	41, 57	87, 93	86, 94	43, 52
	Skin prick test (two studies[165,181])	89, 93	54, 57	79, 81	73, 81
	Specific IgE (three studies[165,166,181])	95, 96, 96	36, 38, 48	75, 79, 79	75, 83, 85
Wheat	Atopy patch test (three studies[162,165,181])	27, 86, 89	35, 89, 94	58, 63, 94	67, 89, 69
	Skin prick test (three studies[162,165,181])	23, 67, 75	53, 64, 100	49, 60, 100	50, 60, 85
	Specific IgE (four studies[162,165,165,181])	20, 67, 80, 82	6, 34, 47, 93	41, 43, 57, 80	25, 45, 57, 77
Soya	Atopy patch test (two studies[165,181])	23, 75	86, 86	30, 50	82, 95
	Skin prick test (two studies[165,181])	29, 50	85, 90	33, 50	82, 90
	Specific IgE (three studies[165,166,181])	65, 75, 100	26, 50, 52	22, 23, 23	86, 92, 100

[a] Data are arranged in numerical order rather than in the study sequence.
[b] One study[161] reported only sensitivity and specificity.

Table C.6 Diagnostic accuracy of tests for detecting any reaction (immediate and/or delayed) to groups of foods using a DBPCFC as the reference test[a]

Allergen	Test	Results (%)			
		Sensitivity	Specificity	PPV	NPV
Cow's milk, egg, wheat, soya	Atopy patch test (two studies[163,164,169])	55, 70	41, 95	45, 93	60, 67
	Skin prick test (one study[163,164])	83	70	79	75
	Specific IgE (three studies[163,164,166,169])	76, 90	29, 63	59, 64	59, 75

[a] Data are arranged in numerical order rather than in the study sequence.

Accuracy according to age

Three studies considered whether the diagnostic accuracy changed with children's age.[166,169,181] The first reported that specificity fell with age,[166] the second found that the sensitivity, specificity, PPV and NPV were lower in children aged 2 years or over compared with those younger than 2 years[169] and the third found that sensitivity increased with age for cow's milk, wheat and soya.[181]

Accuracy according to severity of atopic eczema

No studies considered the diagnostic accuracy results according to the severity of atopic eczema.

Combined tests

Three of the studies described above attempted to consider the accuracy of a combination of tests for any reaction.[161,165,181] Their findings are summarised in Table C.7. They indicate that the PPVs are high when an atopy patch test is combined with a skin prick test and/or IgE.

Diagnostic accuracy of the tests compared with an open oral food challenge

Ten studies compared the diagnostic accuracy of one or more tests (atopy patch test, skin prick test and/or IgE) to an open food challenge test.[171-180] The allergens considered across the studies were cow's milk, egg, peanut and/or cereals. Six considered only one allergen.

In most studies it was not made clear whether the challenge testing was undertaken without knowing the results of the tests being evaluated. All children had atopic eczema; eight of the studies stated that food allergy was suspected as contributing to the children's atopic eczema. One study did not specify whether food allergy was suspected.[176] In another study the children had never ingested egg (the allergen being tested).[175] All studies were considered to be of poor quality because of uncertainty over blinding to the results of other tests, and because an open challenge is not the gold standard for identifying food allergy (in particular, it can introduce bias when reading delayed reactions). [EL = DS III]

Table C.7 Diagnostic accuracy of combined tests for detecting any reaction (immediate and/or delayed) to specific foods using a DBPCFC as the reference test[a]

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

[a] Data are arranged in numerical order rather than in the study sequence.

The age range of children in the studies varied, but in five studies this was within the range of 1 month to 4 years. The age range in the other five studies encompassed children and young people aged from 2 months to 28 years. The total number of children evaluated was 891, ranging from 34 to 146 in individual studies.

Atopic eczema was clear or controlled before the tests were undertaken in six studies (not stated in the remainder). In five studies the suspected food allergen(s) was excluded from the diet for 2–4 weeks before testing.[171,174,177,178,180] Only one study reported that other treatments (topical hydrocortisone) were permitted during the studies.[180] All except two studies[174,180] stated that antihistamines were discontinued before testing (time interval not always reported). Topical corticosteroids were discontinued or prohibited in three studies.[175,178,179]

There was variation in how the food challenges were conducted across the studies. The reporting of the exact type of food tested was generally poor. When the foods used were specified there was variation between the studies (for example, for egg, cooked egg and commercially available egg yolk and egg white were used).

For patch testing, samples were generally left under occlusion for 48 hours and the skin reaction analysed between 15 and 30 minutes after removing the patch, although a reading time of up to 1 hour was reported.[176] In most cases the reaction was also recorded after 72 hours. Positive tests were defined as erythema usually with infiltration. For the skin prick test, a positive test was considered to be a wheal size of 3 mm or greater, or when the area that reacted was a certain size in relation to the histamine reaction (the positive control used). Specific IgE levels were measured using the Pharmacia CAP method, with variation across studies in the levels above which the test was considered to be positive (0.35 ku/l, 0.5 ku/l and 0.70 ku/l all used).

Nine of the studies reported the accuracy of the individual tests for each food allergen separately. The remaining study[173] reported only the accuracy data for all allergens together (cow's milk, egg, peanuts).

One study each reported the accuracy of the tests in diagnosing delayed reactions[171] or immediate reactions.[172] In the other eight studies it was assumed for the guideline that the accuracy data reported represented any reaction on testing. Reporting of what constituted a positive test reaction was generally poor.

The prevalence of food allergy across the studies (that is, the proportion of positive test results on open challenge) ranged from 9% with peanut to 73% with wheat. The proportion of immediate reactions were in the range 3–57% (median 11%) and delayed reactions 21–97% (median 61%), and combined immediate and delayed reactions (reported in one study) 42%. Two studies did not report whether reactions were immediate or delayed. Most did not state whether or what proportion of the delayed reactions manifested as atopic eczema.

Diagnostic accuracy of tests for identifying an immediate reaction

One study reported the diagnostic accuracy of skin prick testing and specific IgE levels for detecting allergy to cow's milk or egg.[172] It was assumed for the guideline that an IgE level of more than 0.35 ku/l was indicative of a positive test, although this was not made explicit in the report (the results were categorised into four groups, the minimum level being 0.35 ku/l). The results are summarised in Table C.8.

Table C.8 Diagnostic accuracy of tests for detecting immediate reactions to specific foods using an open oral food challenge as the reference test

Allergen	Test	Results (%)			
		Sensitivity	Specificity	PPV	NPV
Cow's milk	Skin prick test (one study[172])	88	28	19	92
	Specific IgE (one study[172])	71	56	24	91
Egg	Skin prick test (one study[172])	100	28	23	100
	Specific IgE (one study[172])	90	59	33	96

Diagnostic accuracy of tests for identifying delayed reactions (atopic eczema)
One study considered the accuracy of the atopy patch test to detect a delayed allergic response (exacerbation of atopic eczema in 73%) to cow's milk.[171] Results were reported separately for those aged under and over 3 years and are summarised in Table C.9.

Diagnostic accuracy of tests for identifying any reaction (immediate and/or delayed)
Eight studies reported the diagnostic accuracy of one or more of the tests to detect any response (immediate and/or delayed) to one or more allergens on open food challenge.[172,174–180] One of these reported data when the wheal size of a skin prick test and the IgE level that constituted a positive test were different.[175] The results are summarised in Table C.10.

A further study reported accuracy data for the SAFT test to detect allergy to cow's milk, egg and peanuts; all responses to any of these three allergens were considered together.[173] Details of the tests were poorly reported. The SAFT had sensitivity of 83%, specificity 100%, PPV 100% and NPV 91%.

Accuracy according to age
Two of the studies considered whether the diagnostic accuracy of an atopy patch test for any reaction changed with children's age.[174,176] The first found that sensitivity, specificity and NPV of the test increased with age, while no pattern was evident for the PPV.[174] The second found that the sensitivity and NPV of the test to detect peanut allergy fell with age, while both specificity and PPV increased.[176]

Accuracy according to severity of atopic eczema
No studies considered the diagnostic accuracy results according to the severity of atopic eczema.

Table C.9 Diagnostic accuracy of tests for detecting delayed reactions to specific foods using an oral food challenge as the reference test

Allergen	Test	Results (%)			
		Sensitivity	Specificity	PPV	NPV
Cow's milk	Atopy patch test (children younger than 3 years) (one study[171])	80	70	73	22
	Atopy patch test (children 3 years or over) (one study[171])	80	89	80	11

Table C.10 Diagnostic accuracy of tests for detecting any reactions (immediate and/or delayed) to specific foods using an oral food challenge as the reference test[a]

Allergen	Test	Results (%)			
		Sensitivity	Specificity	PPV	NPV
Cow's milk	Atopy patch test (one study[177])	60	97	95	75
	Skin prick test (three studies[172,177,179])	41, 83, 88	30, 32, 99	46, 47, 96	68, 72, 79
	Specific IgE (one study[172])	59	60	52	67
Egg	Atopy patch test (two studies[174,177])	71, 77	81, 97	65, 96	73, 89
	Skin prick test (four studies[172,174,177,179])	46, 60, 91, 95	32, 38, 93, 97	46, 60, 75, 96	67, 80, 85, 88
	Specific IgE (one study[172])	73	65	57	79
Wheat	Atopy patch test (two studies[177,178])	67, 90	79, 94	90, 92	46, 93
	Skin prick test (three studies[177,178,180])	13, 23, 86	98, 100, 100	80, 100, 100	32, 60, 82
	Specific IgE (one study[180])	93	56	78	83
Peanuts	Atopy patch test (one study[176])	75	87	36	97
	Skin prick test (one study[176])	53	90	25	93

[a] Data arranged in numerical order rather than in the study sequence.

Combined tests

One study reported that the accuracy of a combination of an atopy patch test, skin prick test and specific IgE level compared with an atopy patch test alone was slightly better for children younger than 3 years, but the same for children 3 years or over. (Data for the accuracy of the skin prick test and IgE levels were not reported separately).[171]

Studies that compared different ways of undertaking the same test for food allergy

Several studies have considered whether differences in testing parameters (predominantly the threshold that constitutes a positive test result) affect the diagnostic accuracy of the test being undertaken in children with atopic eczema. These investigations have included the effects of: different chamber size for occlusion, concentrations and vehicles of test materials, and of measuring different symptoms on atopy patch testing; different wheal diameter or composition of foods on skin prick testing; and different IgE levels for specific IgE testing. The findings are described below.

Atopy patch tests

One study investigated whether a smaller chamber size for occlusion during atopy patch testing (6 mm) would have similar diagnostic accuracy to the test using a standard 12 mm chamber (*n* = 30). The foods tested were milk, egg, wheat and soya. The atopy patch test, using both chamber sizes, was compared with a DBPCFC. The sensitivity, PPV and NPV were consistently equivalent or higher with the 12 mm compared with the 6 mm chamber, while the specificity was identical for three of the four allergens; for the remaining allergen the specificity was higher using the 6 mm chamber.[182] [EL = DS III]

Another study considered the effects of conducting an atopy patch test with different vehicles and inhalant allergen concentrations (*n* = 36, age range 3–69 years).[183] It found that generally a higher allergen dose, in petrolatum rather than a hydrogel base, gave more positive reactions. Diagnostic accuracy was not considered. [EL = 3]

In another study the accuracy of different symptoms/signs on atopy patch test (erythema, induration and papules) to diagnose delayed reactions to cow's milk, egg, wheat and soya (relative to DBPCFC) was investigated (*n* = 87).[185] The diagnostic accuracy of the atopy patch test varied with the severity and/or extent of the three parameters measured. The presence of induration and at least seven papules at 72 hours after application of the patch test provided the greatest diagnostic accuracy. [EL = DS Ib]

Skin prick tests

One study considered the accuracy of different wheal sizes as indicators of a positive skin prick test to egg white and egg yolk. The study also reported accuracy data for different IgE levels. The reference standard used was an open food challenge.[175] For both egg white and egg yolk, sensitivity and NPV fell as the wheal size indicative of a positive test increased from 3 mm to 5 mm; conversely the specificity and PPV increased. There was a small difference in sensitivity and NPV for IgE levels of more than 17.5 ku/l or 99 ku/l, while the specificity and PPV were 100% in both cases. [EL = DS III]

Other investigators retrospectively analysed the diagnostic value of absolute wheal size compared with a DBPCFC. For egg and cow's milk, the probability of having a positive test (PPV) on DBPCFC was 95% if the wheal diameters were 13 mm and 12.5 mm, respectively. Predictive probabilities could not be calculated for wheat or soya (*n* = 385, 87% had atopic eczema).[184] [EL = DS III]

The Melbourne milk allergy study reported that all children (median age 3 years) with a skin prick test diameter of more than 8 mm to milk or 7 mm to egg had positive challenge test results (any reaction) to these foods. In children younger than 2 years the wheal diameters associated with positive food challenge results were 6 mm to cow's milk and 5 mm to egg. The proportion of children in this study who had atopic eczema was not reported.[186,187] [EL = 3]

Another short report questioned whether skin prick testing should be undertaken using whole egg or egg white.[188] Median wheal diameter and skin index were greater with egg white than whole egg, but differences were not statistically significant. [EL = 3]

The diagnostic accuracy of crude (fresh) versus commercial allergen extracts for skin prick testing was considered in two studies.[189,190] [EL = DS III] Accuracy relative to a DBPCFC was higher with crude extracts for milk, egg and soya in one study (*n* = 292, mean age 12 years).[189] The second study considered beef, in which sensitivity was higher, and specificity lower with fresh compared with commercial extracts (*n* = 34, median age 2 years).[190]

Immunoglobulin E

One study considered the utility of the food-specific IgE : total IgE ratio in predicting food allergy in children (*n* = 501, 88% of whom had atopic eczema).[191] The specific : total ratio did not improve diagnostic accuracy of IgE testing compared with specific IgE alone. [EL = DS III]

One of the DBPCFC studies also reported accuracy data for specific IgE to cow's milk using two thresholds as indicative of a positive test (0.35 ku/l and 17.5 ku/l). Sensitivity and NPV were higher at the lower threshold (0.35 ku/l); the reverse was true at the threshold of 17.5 ku/l.[165] [EL = DS III]

In one of the studies comparing the accuracy of specific IgE levels with DBPCFC, the IgE levels that would give 90% and 95% predictive values for each of the six foods tested were calculated.[167] The specific IgE levels giving a 95% PPV were 6 ku/l for egg, 32 ku/l for milk, 15 ku/l for peanut and 20 ku/l for fish. The specific IgE levels giving a 90% NPV were 0.6 ku/l for egg, 1.0 ku/l for milk, 5 ku/l for fish (0.9 ku/l for a 95% value), 5 ku/l for soya (2 ku/l for a 95% value) and 79 ku/l for wheat (5 ku/l for a 95% value). [EL = DS III]

The GDG's interpretation of the evidence identified in relation to identification of food allergies is presented in Chapter 6.

Appendix D

Cost-effectiveness of educational interventions for atopic eczema in children

D.1 Background

Educational interventions offered to children with atopic eczema are designed to enhance understanding and management of the disease, to improve concordance with and adherence to treatment and, as a consequence, to improve short- and long-term health outcomes. Education covers everything from basic written information for children with atopic eczema to providing intensive support to engage children and their families/caregivers in managing the condition. All of these interventions require additional scarce healthcare resources. Therefore it is necessary to consider whether the additional costs of education are 'worth' the additional improvements in health outcomes associated with educational interventions in order to persuade providers that they should commit their healthcare resources to such programmes. However, the effectiveness and cost-effectiveness of these interventions have not yet been fully evaluated in the NHS setting.

A high-quality RCT has evaluated an intensive educational programme in Germany.[498] The RCT did not include an economic evaluation and its generalisability to other European countries was not addressed. However, the GDG decided that there was adequate comparability to develop a cost-effectiveness model based on the health outcome data reported in the German RCT. Other scenarios for providing educational programmes more relevant to the NHS were explored using sensitivity analysis.

D.2 The purpose of a cost-effectiveness model

Cost-effectiveness analysis can provide useful information for decision-makers on whether a clinically effective intervention is also a good use of scarce NHS resources. To do this, a cost-effectiveness study requires data on both costs and outcomes. Costs need to reflect the value if an intervention were offered by the NHS and outcomes should preferably be presented in generic units of health gain such as quality-adjusted life years (QALYs). If costs and outcomes are available in this form then it is possible to calculate the incremental cost per QALY ratio (the additional cost per additional QALY gained) for comparison with the equivalent additional cost per QALY ratios for other interventions provided by the NHS (both for atopic eczema and for a wide range of other conditions). A cost per QALY below the NICE threshold for cost-effectiveness of £20,000 per QALY reinforces the argument for an intervention to be provided since it is perceived to be a good use of scarce NHS resources.

D.3 Methods

The cost-effectiveness analysis for educational interventions for atopic eczema in children has two key components: a description of the intervention and the likely cost if it were offered on the NHS; and an estimation of the overall (generic) health gain associated with the intervention.

The German RCT evaluated an age-related structured educational programme offered to children and young people with atopic eczema and their parents. The programme of six once-weekly 2 hour sessions covered information, routine care and treatment, managing symptoms and stress, avoidance of triggers and allergies, and general health. The programme was delivered by one or two healthcare professionals per session who had been trained to offer the programme. The sessions varied slightly depending on the children's age.

After randomisation, the study participants were subdivided according to age (3 months to 7 years, 8–12 years, and 13–18 years) and by severity of disease (SCORAD severity scores) at the time of entry to the trial (a score of 0–14 was classified as mild disease, 15–40 as moderate disease, and over 40 as severe disease).

The participants were followed up for 12 months and the outcomes reported were mean SCORAD scores (and SDs) for children and young people with mild, moderate and severe atopic eczema at baseline and at 12 months, by age group, for the intervention and non-intervention groups.

Cost data

The German RCT provided a detailed description of the structured educational programme that was offered to the children and young people with atopic eczema and their families. Although the content of the sessions differed according to the age of the children, the same healthcare professionals delivered the training to each group (see Table D.1). The programme was offered across seven general and specialist hospitals as part of the RCT.

The cost per hour to the NHS of an equivalent educational programme was calculated using the Unit Costs of Health and Social Care 2006, which provides the midpoint unit cost per hour for NHS staff.[545] (The corresponding costs are based on the Agenda for Change pay scales and not the Whitley scales they replace). The total staff time cost was calculated to be £482 per six-session programme (Table D.1).

The additional costs of providing the educational programme (training the trainers, overheads, and venue and travel costs) were not reported in the German RCT. Therefore a range of additional costs associated with training were estimated for the GDG's analysis to assess what impact they might have on the overall cost-effectiveness of the programme (see below).

Outcome data

The German study presented outcomes in terms of mean severity scores (SCORAD scale), which is of limited value in an economic evaluation. However, a UK study has derived QALY weightings for different health states associated with atopic eczema in children.[113] The UK study developed a preference-based quality of life measure for children with atopic eczema, which resulted in a four-item measure for classifying atopic eczema in children into 16 unique health states. QALY

Table D.1 NHS staff costs for providing an intensive educational programme (six 2 hour sessions) for children with atopic eczema and their parents/caregivers in 2006

Healthcare professional	Cost per hour to the NHS (£)	2 hour cost (£)
Session 1		
Paediatrician/dermatologist	34[a]	68
Psychologist	29	58
Session 2		
Psychologist	29	58
Session 3		
Nurse	24	48
Session 4		
Paediatrician/dermatologist	34	68
Session 5		
Dietitian	28	56
Session 6		
Paediatrician/dermatologist	34	68
Psychologist	29	58
Total (staff only)		**482**

[a] Midpoint on the salary scale for a specialist registrar.

weightings for each health state were derived from a survey of the general public using the standard gamble technique. In this technique an individual has to choose between the certainty of living in a particular health state and an uncertain prospect of two possible outcomes (perfect health or immediate death), each occurring with a specified probability. The probability associated with the second choice is altered until the individual is indifferent between the two choices, at which point the probability is taken to be the QALY value of the particular health state being investigated.

The UK study was considered in the HTA for pimecrolimus and tacrolimus.[291] The HTA took the analysis one step further by defining mild atopic eczema to be any health state with no more than one item in the 'No' category presented in Table D.2. Moderate atopic eczema was defined as two or three items in the 'No' category, and severe atopic eczema as three or four items in the 'No' category. The HTA estimated the QALY values associated with each health state by calculating the average median score (probability value from the public survey[113]) for health states that fell into the mild, moderate and severe categories (see Table D.3).

Converting severity scores into severity categories

The German RCT reported severity (SCORAD) by age group for the intervention group and the control group at baseline and 12 months' follow-up. The thresholds used to convert mean SCORAD scores into mild, moderate and severe categories of atopic eczema were those reported in the 1997 consensus report of the European Task Force on Atopic Eczema (0–14 mild, 15–40 moderate, > 40 severe).[54] Using the mean SCORAD scores (and their SDs) reported in the German RCT, and assuming severity scores were normally distributed, the GDG estimated the percentage of children with mild, moderate and severe atopic eczema in each age group at baseline and at 12 months' follow-up (Table D.4).

Given the eligibility criteria for the German RCT (SCORAD score at least 20), it was known that none of the children or young people were in the mild disease category at baseline. However, without access to patient-level data it was necessary to disaggregate the age-specific data from aggregated mean SCORAD and SDs published in the German RCT. By assuming that SCORAD scores were normally distributed, a proportion of the children in each age group were estimated to be in the mild category at baseline. Therefore, the GDG undertook a sensitivity analysis to explore whether the constraint of only recruiting children with a SCORAD score of at least 20 changed the results of the economic analysis.

Converting severity categories into QALYs

Using the data presented in Table D.4, the number of children in each disease severity category at baseline and 12 months was calculated. The QALY scores associated with mild, moderate and severe atopic eczema (Table D.3) were then applied to the number of children in each

Table D.2 Health state classification developed by Stevens *et al.*[113] (The development of a preference-based measure of health in children with atopic dermatitis, *British Journal of Dermatology*, reproduced with permission from Wiley-Blackwell)

Yes	No
You can't join in some activities with other children	You are not limited in joining in activities with other children
You are very moody	You are not very moody
You cannot be comforted	You are quite settled
You sleep badly most nights	Generally, you sleep very well

Table D.3 Quality of life scores for children with atopic eczema; data from Garside *et al.*[291]

Severity	QALY score
Mild atopic eczema	0.8625
Moderate atopic eczema	0.69
Severe atopic eczema	0.59

Table D.4 Age-stratified disease severity of children receiving education versus no education at baseline and 12 months' follow-up

Age group	Severity	Education			No education		
		No. of children (all severities)	Proportion		No. of children (all severities)	Proportion	
			Baseline	12 months		Baseline	12 months
3 months to 7 years	mild	274	5.79%	30.12%	244	4.61%	20.84%
	moderate		41.57%	53.43%		43.82%	55.06%
	severe		52.64%	16.45%		51.57%	24.10%
8–12 years	mild	102	5.32%	27.09%	83	4.63%	14.31%
	moderate		40.36%	51.79%		44.31%	53.00%
	severe		54.32%	21.12%		51.06%	32.69%
13–18 years	mild	70	2.80%	25.25%	50	3.38%	9.19%
	moderate		38.85%	65.37%		45.47%	53.20%
	severe		58.35%	9.38%		51.15%	37.61%
Total		**446**			**377**		

category to derive a total QALY score by age group for each severity category. From this, the total additional QALYs gained in 12 months was calculated (see Tables D.5 and D.6).

The data indicate that, over a 12 month period, the educational intervention was associated with 17.15 additional QALYs. This can be interpreted as meaning that the intervention produces the same health gain as an additional 17.15 healthy years overall to a population of 446 children and young people who received the educational intervention.

Synthesis of costs and outcomes

To assess whether the health gain associated with the educational intervention is 'worth' the additional cost of the intervention, it was necessary to synthesise the costs and outcomes. Assuming that six or seven children (or young people) would attend each educational programme (the GDG's collective experience suggested that this would be feasible/realistic), a maximum of 64–75 sessions would have been required for the sample of 446 children and young people involved in the German RCT. At a staff cost of £482 per six-session programme, the total staff cost of implementing an educational programme in the NHS on the scale of the German RCT would be around £36,000 (assuming six children (or young people) per session).

Since the GDG had no information about the additional costs of providing training, the approach taken for the guideline was to estimate the upper limit for the additional costs that would ensure cost-effectiveness of the programme using the NICE threshold of £20,000 per QALY. Using the threshold of £20,000 per QALY, the education programme would be judged to be cost-effective provided that the total cost did not exceed £343,000 (17.15 × £20,000). If the additional costs were less than, say, £300,000 (that is, under £4,000 for each six-session programme) then the intervention would still be cost-effective, within the assumptions of the model. This means that if the cost of an educational programme in the NHS was less than £769 per child (or young person) and as effective as the programme evaluated in the German RCT then the programme would be cost-effective. Given a total staff cost of around £36,000 and additional costs of at most £300,000, the cost per child would be £753, making the educational intervention cost-effective.

D.4 Sensitivity analysis

Sensitivity analysis was undertaken to assess the importance of assumptions made in the economic analysis. First, the German RCT reported that a SCORAD score of at least 20 was one of the inclusion criteria for the study (that is, no children or young people had mild atopic eczema at baseline). Sensitivity analysis was undertaken to assess the effects of assuming that no children had mild atopic eczema in the study. This is not entirely consistent with the normality assumption because it implies a 95% confidence interval that is not symmetric about the mean (that is, it

Table D.5 Age-specific QALYs at baseline and 12 months' follow-up

Age group	Severity	Education				No education			
		Baseline		12 months		Baseline		12 months	
		n	QALYs	*n*	QALYs	*n*	QALYs	*n*	QALYs
3 months to 7 years	mild	16	13.68	83	71.18	11	9.70	51	43.86
	moderate	114	78.59	146	101.01	107	73.78	134	92.70
	severe	144	85.10	45	26.59	126	74.24	59	34.69
Total for 3 months to 7 years			**177.37**		**198.79**		**157.72**		**171.25**
8–12 years	mild	5	4.68	28	23.83	4	3.31	12	10.24
	moderate	41	28.41	53	36.45	37	25.38	44	30.35
	severe	55	32.69	22	12.71	42	25.00	27	16.01
Total for 8–12 years			**65.78**		**72.99**		**53.69**		**56.61**
13–18 years	mild	2	1.69	18	15.24	2	1.46	5	3.96
	moderate	27	18.76	46	31.57	23	15.69	27	18.35
	severe	41	24.10	7	3.87	26	15.09	19	11.09
Total for 13–18 years			**44.55**		**50.69**		**32.23**		**33.41**

Table D.6 Additional QALYs gained over 12 months

Age group	Education	No education
3 months to 7 years	21.42	13.53
8–12 years	7.22	2.91
13–18 years	6.14	1.18
Total QALYs gained	**34.77**	**17.62**
Additional QALYs associated with the educational programme	**17.15**	

ignores the possibility of SCORAD < 20 for a given mean and SD). The sensitivity analysis showed that this constraint was not an important factor to consider in the cost-effectiveness analysis since it did not have a big effect on the outcome (Table D.7).

Sensitivity analysis was also undertaken using different QALY values for mild, moderate and severe atopic eczema. The HTA published QALY values derived from a pilot project to estimate QALY values for health states from the general public. The pilot project, which was described in full in a subsequent publication,[546] consisted of a panel of 15 lay representatives who met regularly to value health states from disease-specific scenarios. The data obtained from the pilot project should be interpreted with caution, but they provide an alternative set of QALY values (derived using a different methodology) to consider in the economic analysis for education. The values derived from the utility panel for atopic eczema were 0.985 for mild disease, 0.875 for moderate disease, and 0.59 for severe disease. Using these values, and assuming a SCORAD score of at least 20 at baseline, the cost-effectiveness of early educational intervention was even greater (Table D.8).

D.5 Model assumptions and limitations

Outcomes

All children with a minimum duration of disease of 3 months and a SCORAD score of at least 20 were eligible for the German RCT. The study was undertaken across seven centres specialising in children's services, dermatology or 'psychosomatic medicine'. Therefore, the study population reflected the proportion of children with atopic eczema in these (secondary care) settings. Only a small proportion of children with atopic eczema are cared for in a secondary care setting and, therefore, the economic analysis does not address the cost-effectiveness of educational

Table D.7 Additional QALYs gained over 12 months assuming SCORAD ≥ 20 at baseline

Age group	Education	No education
3 months to 7 years	24.15	15.47
8–12 years	8.15	3.57
13–18 years	6.48	1.47
Total QALYs gained	**38.78**	**20.52**
Additional QALYs associated with the educational programme	**18.27**	

Table D.8 Additional QALYs gained over 12 months using QALY values derived from the Utility Panel Pilot Project[546]

Age group	Education	No education
3 months to 7 years	28.91	19.00
8–12 years	9.81	4.36
13–18 years	8.80	1.86
Total QALYs gained	**47.52**	**25.21**
Additional QALYs associated with the educational programme	**22.31**	

interventions for children with milder disease who are cared for in other settings (community and/or primary care).

Sample attrition may be an important issue since the loss to follow-up was higher in the control group than in the intervention group (control group 199 versus intervention group 50). If those children and young people who were lost to follow-up in the control group had milder disease then the effectiveness of the intervention would be reduced. Without patient-level data it is not possible to determine whether this was the case.

The use of the QALY values from the UK study[113] formed an important assumption since this was just one study with a relatively small survey sample of the general public who may not have had any experience of living with atopic eczema or caring for a child with the condition. The additional assumption made in the HTA to attach QALY values to levels of severity of atopic eczema in children was not based on empirical evidence and has not been validated in any quality of life studies. However, the QALY values reported in the HTA do appear to be consistent with other reported QALY values for children with atopic eczema. The Health Outcomes Data Repository (HODaR) in Cardiff University which holds data on QALY values classified according to the tenth edition of the International Classification of Diseases (ICD-10) includes a value of 0.666 for dermatitis (type unspecified), which is between the values for moderate and severe atopic eczema in children reported by Stevens.[113]

Costs

The cost data considered here were for staff only, and the GDG has valued the time for the same healthcare professionals as described in the German RCT. However, in the NHS, other healthcare professionals might take these roles and this could alter the costs. Nevertheless, given that the analysis indicated that education is well below the NICE threshold for cost-effectiveness of £20,000 per QALY, using staff from a higher pay grade would not alter the overall cost-effectiveness of the intervention.

Applicability to the NHS setting

It is not realistic to assume that an educational programme run by such a diverse multidisciplinary team as that involved in the German RCT would be immediately transferable to the NHS. It is more likely that such a programme would be delivered by specialist nurses or consultant nurses in dermatology clinics. The cost of delivering such a programme of education would be less if it were delivered exclusively by this professional group (the staff costs would fall to around £384 assuming a nurse consultant costs around £32 per hour based on the Agenda for Change midpoint salary scale for

Band 7 in April 2005). The educational intervention described in the German RCT was a 2 hour, six-session programme. There is no evidence of the effectiveness of less resource-intensive (less expensive) educational interventions, but if an intensive educational intervention delivered by specialist nurses provided some additional benefits (even if they were not on the scale of those associated with an intensive programme) then that might still be cost-effective. For example, if each course was run by specialist nurses and had only half the additional overhead costs (say £150,000 for the total educational programme), but accrued only half the QALYs of an intensive programme then, using the baseline assumptions, it would still be within the £20,000 per QALY cut-off for cost-effectiveness used by NICE. The cost of overheads is very unlikely to be £150,000. It would be more realistic for the NHS to assume that the overhead costs might be around £50,000 to deliver the programme to around 500 children with atopic eczema. If the course were delivered by a specialist nurse over six sessions and to a larger group of children (say ten per group, requiring a total of 45 groups for 446 children) and if the effectiveness was a quarter of that calculated for the German educational programme then it is highly probable that this would still be a cost-effective intervention (Table D.9).

Table D.9 Cost per QALY over 12 months assuming the programme has lower costs and reduced effectiveness compared with the German programme

Educational programme content	Value
Specialist nurse consultant (2 hour cost)	£64
Cost of six sessions	£384
Total staff costs for 45 six-session courses	£17,280
Other overhead costs	£50,000
Total cost	£67,280
QALYs gained assuming the programme were only 25% as effective as the German programme	4.29
Cost per QALY gained	**£15,693**

D.6 Conclusion

There were very few empirical data on the effectiveness of educational interventions for children with atopic eczema. No studies that compared different educational models were identified and therefore there is a lack of knowledge about what type of educational model (if any) would be optimal. The clinical evidence that was identified came from one high-quality German RCT. However, no economic analysis was undertaken as part of that study. A cost-effectiveness analysis was undertaken by the GDG using the outcome data from the German RCT and data from a UK study on the QALY values associated with mild, moderate and severe atopic eczema in children. Using 2005/06 UK cost data for NHS staff time and estimating the additional costs of training, the GDG calculated the additional cost per QALY of providing an intensive educational programme for children with atopic eczema in secondary care in the NHS. The baseline data indicated that, if an educational programme similar to that described in the German RCT could be provided at a cost of less than around £800 per child, then it would be highly likely to be cost-effective. Sensitivity analyses were performed by varying costs and outcome values (SCORAD scores and QALYs) and considering different assumptions. This resulted in cost-effectiveness ratios that were favourable to educational interventions. Furthermore, even though an educational programme such as that described in the German RCT would be unlikely to be implemented in the NHS in the near future, a less resource-intensive and less effective programme that could be implemented in the NHS would probably be cost-effective, based on the sensitivity analysis results and GDG expert opinion that the more resource-intensive multidisciplinary approach would yield little additional benefit in the 85% of patients with mild to moderate eczema compared with a similar but less resource-intensive programme delivered in the NHS.

Although education is a non-clinical intervention, it appears to be both effective and good value for money; it could be a worthwhile area of focus for services for children with atopic eczema in secondary care. Empirical evidence of its value in NHS secondary care settings and for children managed in primary care settings would strengthen this conclusion.

References

1. Hanifin JM, Cooper KD, Ho VC, *et al.* Guidelines of care for atopic dermatitis. *Journal of the American Academy of Dermatology* 2004;50(3):391–404.
2. Friedmann PS, Holden CA. Atopic dermatitis. In: Burns DA, Braethnach SM, Cox N, Griffiths CE, eds. *Rook's Textbook of Dermatology*. 7th ed. Blackwell Publishers; 2004.
3. Herd RM, Tidman MJ, Prescott RJ, *et al.* The cost of atopic eczema. *British Journal of Dermatology* 1996;135(1):20–3.
4. Emerson RM, Williams HC, Allen BR. What is the cost of atopic dermatitis in preschool children? *British Journal of Dermatology* 2001;144(3):514–22.
5. Weinmann S, Kamtsiuris P, Henke KD, *et al.* The costs of atopy and asthma in children: assessment of direct costs and their determinants in a birth cohort. *Pediatric Allergy and Immunology* 2003;14(1):18–26.
6. Ricci G. Atopic dermatitis in Italian children: evaluation of its economic impact. *Journal of Pediatric Health Care* 2006;20(5):311–15.
7. Su JC, Kemp AS, Varigos GA, *et al.* Atopic eczema: its impact on the family and financial cost. *Archives of Disease in Childhood* 1997;76(2):159–62.
8. Barbeau M, Lalonde H. Burden of atopic dermatitis in Canada. *International Journal of Dermatology* 2006;45(1):31–6.
9. Verboom P, Hakkaart-Van RL, Sturkenboom M, *et al.* The cost of atopic dermatitis in the Netherlands: An international comparison. *British Journal of Dermatology* 2002;147(4):716–24.
10. NHS Executive. *Clinical Guidelines: Using Clinical Guidelines to Improve Patient Care Within the NHS.* London: HMSO; 1996.
11. National Institute for Clinical Excellence. Referral Advice. 2001.
12. National Institute for Clinical Excellence. *Frequency of Application of Topical Corticosteroids for Atopic Eczema.* London: NICE; 2004.
13. National Institute for Clinical Excellence. *Tacrolimus and Pimecrolimus for Atopic Eczema.* London: NICE; 2004.
14. National Institute for Clinical Excellence. *Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers.* London: NICE; 2005.
15. National Institute for Health and Clinical Excellence. *The Guidelines Manual 2006.* London: NICE; 2006.
16. National Institute for Health and Clinical Excellence. *The Guidelines Manual 2007.* London: NICE; 2007.
17. Oxman AD, Sackett DL, Guyatt GH. Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group. *JAMA: the Journal of the American Medical Association* 1993;270(17):2093–5.
18. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA: the Journal of the American Medical Association* 1993;270(21):2598–601.
19. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. *JAMA: the Journal of the American Medical Association* 1994;271(1):59–63.
20. Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA: the Journal of the American Medical Association* 1994;271(5):389–91.
21. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA: the Journal of the American Medical Association* 1994;271(9):703–7.
22. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine. How to Practice and Teach EBM.* 2nd ed. Edinburgh: Churchill Livingstone; 2000.
23. Scottish Intercollegiate Guidelines Network. *SIGN 50: A Guideline Developers' Handbook.* No. 50. Edinburgh: SIGN; 2001.
24. Drummond MF, Sculpher M, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes.* 3rd ed. Oxford: Oxford University Press; 2005.
25. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermato-Venereologica* 1980;(Suppl 92):44–7.
26. Hoare C, Li Wan PA, Williams H. Systematic review of treatments for atopic eczema. *Health Technology Assessment* 2000;4(37):1–191.
27. Williams HC, Burney PG, Hay RJ, *et al.* The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *British Journal of Dermatology* 1994;131(3):383–96.
28. Williams HC, Burney PG, Pembroke AC, *et al.* The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. *British Journal of Dermatology* 1994;131(3):406–16.
29. Williams HC, Burney PG, Strachan D, *et al.* The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. II. Observer variation of clinical diagnosis and signs of atopic dermatitis. *British Journal of Dermatology* 1994;131(3):397–405.
30. Williams HC, Burney PGJ, Pembroke AC, *et al.* Validation of the U.K. diagnostic criteria for atopic dermatitis in a population setting. *British Journal of Dermatology* 1996;135(1):12–17.
31. Popescu CM, Popescu R, Williams H, *et al.* Community validation of the United Kingdom diagnostic criteria for atopic dermatitis in Romanian schoolchildren. *British Journal of Dermatology* 1998;138(3):436–42 [erratum appears in *Br J Dermatol* 1998;139(3):564].
32. Chalmers DA, Todd G, Saxe N, *et al.* Validation of the U.K. Working Party diagnostic criteria for atopic eczema in a Xhosa-speaking African population. *British Journal of Dermatology* 2007;156(1):111–16.
33. Fleming S, Bodner C, Devereux G, *et al.* An application of the United Kingdom Working Party diagnostic criteria for atopic dermatitis in Scottish infants. *Journal of Investigative Dermatology* 2001;117(6):1526–30.
34. De D. Comparative efficacy of Hanifin and Rajka's criteria and the UK working party's diagnostic criteria in diagnosis of atopic dermatitis in a hospital setting in North India. *Journal of the European Academy of Dermatology and Venereology* 2006;20(7):853–9.
35. Firooz A, Davoudi SM, Farahmand AN, *et al.* Validation of the diagnostic criteria for atopic dermatitis. *Archives of Dermatology* 1999;135(5):514–16.

36. Gu H, Chen XS, Chen K, *et al.* Evaluation of diagnostic criteria for atopic dermatitis: validity of the criteria of Williams, *et al.* in a hospital-based setting. *British Journal of Dermatology* 2001;145(3):428–33.
37. Charman C. *Measuring Atopic Eczema Severity: Improving Outcome Measures for Research and Clinical Practice.* Thesis. University of Nottingham; 2005.
38. Finlay AY. Measurement of disease activity and outcome in atopic dermatitis. *British Journal of Dermatology* 1996;135(4):509–15.
39. Charman C, Williams H. Outcome measures of disease severity in atopic eczema. *Archives of Dermatology* 2000;136(6):763–9.
40. Charman C, Chambers C, Williams H. Measuring atopic dermatitis severity in randomized controlled clinical trials: what exactly are we measuring? *Journal of Investigative Dermatology* 2003;120(6):932–41.
41. Charman D, Varigos G, Horne DJ, *et al.* The development of a practical and reliable assessment measure for atopic dermatitis (ADAM). *Journal of Outcome Measurement* 1999;3(1):21–34.
42. Charman DP, Varigos GA. Grades of severity and the validation of an atopic dermatitis assessment measure (ADAM). *Journal of Outcome Measurement* 1999;3(2):162–75.
43. Verwimp JJ, Bindels JG, Barents M, *et al.* Symptomatology and growth in infants with cow's milk protein intolerance using two different whey-protein hydrolysate based formulas in a Primary Health Care setting. *European Journal of Clinical Nutrition* 1995; 49(Suppl 1): S39–48.
44. Costa C, Rilliet A, Nicolet M, *et al.* Scoring atopic dermatitis: the simpler the better? *Acta Dermato-Venereologica* 1989;69(1):41–5.
45. Tofte S, Graeber M, Cherill M, Omoto M, Thurston M, Hanifin JM. Eczema area and severity index (EASI): A new tool to evaluate atopic dermatitis. [Abstract] *Journal of the European Academy of Dermatology and Venereology* 1998;11(Suppl 2):S197.
46. Housman TS, Patel MJ, Camacho F, *et al.* Use of the Self-Administered Eczema Area and Severity Index by parent caregivers: results of a validation study. *British Journal of Dermatology* 2002;147(6):1192–8.
47. Barbier N. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. *British Journal of Dermatology* 2004;150(1):96–102.
48. Emerson RM, Charman CR, Williams HC. The Nottingham Eczema Severity Score: preliminary refinement of the Rajka and Langeland grading. *British Journal of Dermatology* 2000;142(2):288–97.
49. Hon KL, Ma KC, Wong E, *et al.* Validation of a self-administered questionnaire in Chinese in the assessment of eczema severity. *Pediatric Dermatology* 2003;20(6):465–9.
50. Sugarman JL, Fluhr JW, Fowler AJ, *et al.* The objective severity assessment of atopic dermatitis score: an objective measure using permeability barrier function and stratum corneum hydration with computer-assisted estimates for extent of disease. *Archives of Dermatology* 2003;139(11):1417–22.
51. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Archives of Dermatology* 2004;140(12):1513–19.
52. Berth-Jones J. Six area, six sign atopic dermatitis (SASSAD) severity score: a simple system for monitoring disease activity in atopic dermatitis. *British Journal of Dermatology* 1996;135(Suppl 48):25–30.
53. Stalder JF, Taieb A, Atherton DJ, *et al.* Severity scoring of atopic dermatitis: The SCORAD index. Consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1993;186(1):23–31.
54. Kunz B, Oranje AP, Labreze L, *et al.* Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997;195(1):10–19.
55. Wolkerstorfer A, De Waard van der Spek FB, Glazenburg EJ, *et al.* Scoring the severity of atopic dermatitis: three item severity score as a rough system for daily practice and as a pre-screening tool for studies. *Acta Dermato-Venereologica* 1999;79(5):356–9.
56. Lob-Corzilius T, Boer S, Scheewe S, *et al.* The 'Skin Detective Questionnaire': A survey tool for self-assessment of patients with atopic dermatitis. First results of its application. *Dermatology and Psychosomatics* 2004;5(3):141–6.
57. Sprikkelman AB, Tupker RA, Burgerhof H, *et al.* Severity scoring of atopic dermatitis: a comparison of three scoring systems. *Allergy* 1997;52(9):944–9.
58. Queille-Roussel C, Raynaud F, Saurat JH. A prospective computerized study of 500 cases of atopic dermatitis in childhood. I. Initial analysis of 250 parameters. *Acta Dermato-Venereologica* 1985; 114(Suppl):87–92.
59. Hanifin JM, Thurston M, Omoto M, *et al.* The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Experimental Dermatology* 2001;10(1):11–18.
60. Balkrishnan R, Housman TS, Carroll C, *et al.* Disease severity and associated family impact in childhood atopic dermatitis. *Archives of Disease in Childhood* 2003;88(5):423–7.
61. Hon KL, Leung TF, Ma KC, *et al.* Urinary leukotriene E4 correlates with severity of atopic dermatitis in children. *Clinical and Experimental Dermatology* 2004;29(3):277–81.
62. Charman CR, Venn AJ, Williams HC. Reliability testing of the Six Area, Six Sign Atopic Dermatitis severity score. *British Journal of Dermatology* 2002;146(6):1057–60.
63. Berth-Jones J, Arkwright PD, Marasovic D, *et al.* Killed *Mycobacterium vaccae* suspension in children with moderate-to-severe atopic dermatitis: a randomized, double-blind, placebo-controlled trial. *Clinical and Experimental Allergy* 2006;36:1115–21.
64. Berth-Jones J, Finlay AY, Zaki I, *et al.* Cyclosporine in severe childhood atopic dermatitis: a multicenter study. *Journal of the American Academy of Dermatology* 1996;34(6):1016–21.
65. Berth-Jones J, Graham-Brown RA. Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. *Lancet* 1993;341(8860):1557–60 [erratum appears in *Lancet* 1993;342(8870):564].
66. Berth-Jones J, Thompson J, Graham-Brown RA. Evening primrose oil and atopic eczema. *Lancet* 1995;345(8948):520.
67. van Joost T, Kozel MM, Tank B, *et al.* Cyclosporine in atopic dermatitis. Modulation in the expression of immunologic markers in lesional skin. *Journal of the American Academy of Dermatology* 1992; 27(6 Pt 1):922–8.
68. Chamlin SL, Kao J, Frieden IJ, *et al.* Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *Journal of the American Academy of Dermatology* 2002;47(2):198–208.
69. Bringhurst C, Waterston K, Schofield O, *et al.* Measurement of itch using actigraphy in pediatric and adult populations. *Journal of the American Academy of Dermatology* 2004;51(6):893–8.
70. Pucci N, Novembre E, Cammarata MG, *et al.* Scoring atopic dermatitis in infants and young children: distinctive features of the SCORAD index. *Allergy* 2005;60(1):113–16.
71. Hon KL, Leung TF, Wong. Lesson from performing SCORADs in children with atopic dermatitis: subjective symptoms do not correlate well with disease extent or intensity. *International Journal of Dermatology* 2006;45(6):728–30.

72. Schafer T, Dockery D, Kramer U, *et al.* Experiences with the severity scoring of atopic dermatitis in a population of German pre-school children. *British Journal of Dermatology* 1997;137(4):558–62.
73. Oranje AP, Stalder JF, Taieb A, *et al.* Scoring of atopic dermatitis by SCORAD using a training atlas by investigators from different disciplines. ETAC Study Group. Early Treatment of the Atopic Child. *Pediatric Allergy and Immunology* 1997;8(1):28–34.
74. Ben-Gashir MA, Seed PT, Hay RJ. Are quality of family life and disease severity related in childhood atopic dermatitis? *Journal of the European Academy of Dermatology and Venereology* 2002;16(5):455–62.
75. Ben-Gashir MA, Seed PT, Hay RJ. Quality of life and disease severity are correlated in children with atopic dermatitis. *British Journal of Dermatology* 2004;150(2):284–90.
76. Charman CR, Venn AJ, Williams H. Measuring atopic eczema severity visually: which variables are most important to patients? *Archives of Dermatology* 2005;141(9):1146–51.
77. Charman C, Venn AJ, Williams HC. Measurement of body surface area involvement in atopic eczema: an impossible task? *British Journal of Dermatology* 1999;140(1):109–11.
78. Tripodi S, Panetta V, Pelosi S, *et al.* Measurement of body surface area in atopic dermatitis using specific PC software (ScoradCard). *Pediatric Allergy and Immunology* 2004;15(1):89–92.
79. Holm EA, Jemec GB. Time spent on treatment of atopic dermatitis: a new method of measuring pediatric morbidity? *Pediatric Dermatology* 2004;21(6):623–7.
80. Ben-Gashir MA, Hay RJ. Reliance on erythema scores may mask severe atopic dermatitis in black children compared with their white counterparts. *British Journal of Dermatology* 2002;147(5):920–5.
81. Absolon CM, Cottrell D, Eldridge SM, *et al.* Psychological disturbance in atopic eczema: the extent of the problem in school-aged children. *British Journal of Dermatology* 1997;137(2):241–5.
82. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): Initial validation and practical use. *British Journal of Dermatology* 1995;132(6):942–9.
83. Daud LR, Garralda ME, David TJ. Psychosocial adjustment in preschool children with atopic eczema. *Archives of Disease in Childhood* 1993;69(6):670–6.
84. Sarkar R, Raj L, Kaur H, *et al.* Psychological disturbances in Indian children with atopic eczema. *Journal of Dermatology* 2004;31(6):448–54.
85. Walker C, Papadopoulos L, Hussein M, *et al.* Paediatric eczema, illness beliefs and psychosocial morbidity: How does eczema affect children (in their own words)? *Dermatology and Psychosomatics* 2004;5(3):126–31.
86. Andreoli E, Mozzetta A, Palermi G, *et al.* Psychological diagnosis in pediatric dermatology. *Dermatology and Psychosomatics* 2002;3(3):139–43.
87. Moore K, David TJ, Murray CS, *et al.* Effect of childhood eczema and asthma on parental sleep and well-being: A prospective comparative study. *British Journal of Dermatology* 2006;154(3):514–18.
88. Ricci G, Bendandi B, Aiazzi R, *et al.* Educational and medical programme for young children affected by atopic dermatitis and for their parents. *Dermatology and Psychosomatics* 2004;5(4):187–92.
89. Dennis H. Factors promoting psychological adjustment to childhood atopic eczema. *Journal of Child Health Care* 2006;10(2):126–39.
90. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *British Journal of Dermatology* 2006;155(1):145–51.
91. Elliott BE, Luker K. The experiences of mothers caring for a child with severe atopic eczema. *Journal of Clinical Nursing* 1997;6(3):241–7.
92. Lawson V, Lewis-Jones MS, Finlay AY, *et al.* The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. *British Journal of Dermatology* 1998;138(1):107–13.
93. Reid P, Lewis-Jones MS. Sleep difficulties and their management in preschoolers with atopic eczema. *Clinical and Experimental Dermatology* 1995;20(1):38–41.
94. Long CC, Funnell CM, Collard R, *et al.* What do members of the National Eczema Society really want? *Clinical and Experimental Dermatology* 1993;18(6):516–22.
95. Paller AS, McAlister RO, Doyle JJ, *et al.* Perceptions of physicians and pediatric patients about atopic dermatitis, its impact, and its treatment. *Clinical Pediatrics* 2002;41(5):323–32.
96. Zuberbier T, Orlow SJ, Paller AS, *et al.* Patient perspectives on the management of atopic dermatitis. *Journal of Allergy and Clinical Immunology* 2006;118(1):226–32.
97. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *International Journal of Clinical Practice* 2006;60(8):984–92.
98. Warschburger P, Buchholz HT, Petermann F. Psychological adjustment in parents of young children with atopic dermatitis: which factors predict parental quality of life? *British Journal of Dermatology* 2004;150(2):304–11.
99. von Ruden U, Bunikowski R, Brautigam M, *et al.* Cyclosporin A treatment of children with severe atopic dermatitis improves quality of life of their mothers. *Dermatology and Psychosomatics* 2002;3(1):14–18.
100. Wenninger K, Kehrt R, von RU, *et al.* Structured parent education in the management of childhood atopic dermatitis: the Berlin model. *Patient Education and Counseling* 2000;40(3):253–61.
101. Staab D, von Rueden U, Kehrt R, *et al.* Evaluation of a parental training program for the management of childhood atopic dermatitis. *Pediatric Allergy and Immunology* 2002;13(2):84–90.
102. Lewis-Jones MS, Finlay AY, Dykes PJ. The infants' dermatitis quality of life index. *British Journal of Dermatology* 2001;144(1):104–10.
103. Beattie PE, Lewis-Jones MS. An audit of the impact of a consultation with a paediatric dermatology team on quality of life in infants with atopic eczema and their families: further validation of the Infants' Dermatitis Quality of Life Index and Dermatitis Family Impact score. *British Journal of Dermatology* 2006;155(6):1249–55.
104. Aziah MS, Rosnah T, Mardziah A, *et al.* Childhood atopic dermatitis: a measurement of quality of life and family impact. *Medical Journal of Malaysia* 2002;57(3):329–39.
105. Hon KLE, Kam WYC, Lam MCA, *et al.* CDLQI, SCORAD and NESS: Are they correlated? *Quality of Life Research* 2006;15(10):1551–8.
106. Holme SA, Man I, Sharpe JL, *et al.* The Children's Dermatology Life Quality Index: validation of the cartoon version. *British Journal of Dermatology* 2003;148(2):285–90.
107. McKenna SP, Whalley D, Dewar AL, *et al.* International development of the Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD). *Quality of Life Research* 2005;14(1):231–41.

108. Meads DM, McKenna SP, Kahler K. The quality of life of parents of children with atopic dermatitis: interpretation of PIQoL-AD scores. *Quality of Life Research* 2005;14(10):2235–45.

109. McKenna SP, Whalley D, De PY, *et al.* Treatment of paediatric atopic dermatitis with pimecrolimus (Elidel, SDZ ASM 981): Impact on quality of life and health-related quality of life. *Journal of the European Academy of Dermatology and Venereology* 2006;20(3):248–54.

110. Staab D, Kaufmann R, Brautigam M, *et al.* Treatment of infants with atopic eczema with pimecrolimus cream 1% improves parents' quality of life: A multicenter, randomized trial. *Pediatric Allergy and Immunology* 2005;16(6):527–33.

111. Chamlin SL, Frieden IJ, Williams ML, *et al.* Effects of atopic dermatitis on young American children and their families. *Pediatrics* 2004;114(3):607–11.

112. Chamlin SL, Cella D, Frieden IJ, *et al.* Development of the Childhood Atopic Dermatitis Impact Scale: initial validation of a quality-of-life measure for young children with atopic dermatitis and their families. *Journal of Investigative Dermatology* 2005;125(6):1106–11.

113. Stevens KJ, Brazier JE, McKenna SP, *et al.* The development of a preference-based measure of health in children with atopic dermatitis. *British Journal of Dermatology* 2005;153(2):372–7.

114. Charman CR, Williams HC. Epidemiology. In: Bieber T, Leung DYM, eds. *Atopic Dermatitis*. New York: Dekker; 2002. p. 21–42.

115. Williams H. The natural history of atopic eczema. In: Williams H, ed. *Atopic Dermatitis: the Epidemiology, Causes and Prevention of Atopic Eczema*. Cambridge: Cambridge University Press; 2000. p. 41–59.

116. Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. *British Medical Journal* 1992;304(6831):873–5 [erratum appears in *BMJ* 1992;304(6835):1157].

117. Burr ML, Wat D, Evans C, *et al.* Asthma prevalence in 1973, 1988 and 2003. *Thorax* 2006;61(4):296–9.

118. Heinrich J, Hoelscher B, Frye C, *et al.* Trends in prevalence of atopic diseases and allergic sensitization in children in Eastern Germany. *European Respiratory Journal* 2002;19(6):1040–6.

119. Olesen AB, Bang K, Juul S, *et al.* Stable incidence of atopic dermatitis among children in Denmark during the 1990s. *Acta Dermato-Venereologica* 2005;85(3):244–7.

120. Selnes A, Bolle R, Holt J, *et al.* Cumulative incidence of asthma and allergy in north-Norwegian schoolchildren in 1985 and 1995. *Pediatric Allergy and Immunology* 2002;13(1):58–63.

121. Yura A, Shimizu T. Trends in the prevalence of atopic dermatitis in school children: longitudinal study in Osaka Prefecture, Japan, from 1985 to 1997. *British Journal of Dermatology* 2001;145(6):966–73.

122. Kay J, Gawkrodger DJ, Mortimer MJ, *et al.* The prevalence of childhood atopic eczema in a general population. *Journal of the American Academy of Dermatology* 1994;30(1):35–9.

123. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *British Journal of Dermatology* 1998;139(1):73–6.

124. Williams H, Robertson C, Stewart A, *et al.* Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *Journal of Allergy and Clinical Immunology* 1999;103(1 Pt 1):125–38.

125. Bieber T. *Atopic Dermatitis*. New York, Basel: Marcel Dekker; 2002.

126. Kurukulaaratchy R, Fenn M, Matthews S, *et al.* The prevalence, characteristics of and early life risk factors for eczema in 10-year-old children. *Pediatric Allergy and Immunology* 2003;14(3):178–83.

127. Harris JM. Early allergen exposure and atopic eczema. *British Journal of Dermatology* 2007;156(4):698–704.

128. McNally NJ, Williams HC, Phillips DR, *et al.* Is there a geographical variation in eczema prevalence in the UK? Evidence from the 1958 British Birth Cohort Study. *British Journal of Dermatology* 2000;142(4):712–20.

129. George S, Berth-Jones J, Graham-Brown RA. A possible explanation for the increased referral of atopic dermatitis from the Asian community in Leicester. *British Journal of Dermatology* 1997;136(4):494–7.

130. Williams HC, Pembroke AC, Forsdyke H, *et al.* London-born black Caribbean children are at increased risk of atopic dermatitis. *Journal of the American Academy of Dermatology* 1995;32(2 Pt 1):212–17.

131. Wadonda-Kabondo N, Sterne JA, Golding J, *et al.* A prospective study of the prevalence and incidence of atopic dermatitis in children aged 0–42 months. *British Journal of Dermatology* 2003;149(5):1023–8.

132. Williams HC, Strachan DP. The natural history of childhood eczema: Observations from the British 1958 birth cohort study. *British Journal of Dermatology* 1998;139(5):834–9.

133. Ben-Gashir MA, Seed PT, Hay RJ. Predictors of atopic dermatitis severity over time. *Journal of the American Academy of Dermatology* 2004;50(3):349–56.

134. Illi S, von Mutius E, Lau S, *et al.*; Multicenter Allergy Study Group. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *Journal of Allergy and Clinical Immunology* 2004;113(5):925–31.

135. Aoki T, Fukuzumi T, Adachi J, *et al.* Re-evaluation of skin lesion distribution in atopic dermatitis. Analysis of cases 0 to 9 years of age. *Acta Dermato-Venereologica* 1992;176(Suppl):19–23.

136. Nnoruka EN. Current epidemiology of atopic dermatitis in south-eastern Nigeria. *International Journal of Dermatology* 2004;43(10):739–44.

137. Macharia WM, Anabwani GM, Owili DM. Clinical presentation of atopic dermatitis in Negroid children. *African Journal of Medicine and Medical Sciences* 1993;22(4):41–4.

138. Bohme M, Lannero E, Wickman M, *et al.* Atopic dermatitis and concomitant disease patterns in children up to two years of age. *Acta Dermato-Venereologica* 2002;82(2):98–103.

139. Bergmann RL, Bergmann KE, Lau-Schadensdorf S, *et al.* Atopic diseases in infancy. The German multicenter atopy study (MAS-90). *Pediatric Allergy and Immunology* 1994; 5(6 Suppl):19–25.

140. Kulig M, Bergmann R, Klettke U, *et al.* Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *Journal of Allergy and Clinical Immunology* 1999;103(6):1173–9.

141. Bergmann RL, Edenharter G, Bergmann KE, *et al.* Atopic dermatitis in early infancy predicts allergic airway disease at 5 years. *Clinical and Experimental Allergy* 1998;28(8):965–70.

142. Eigenmann P, Calza, A-M. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis. *Pediatric Allergy and Immunology* 2000;11:95–100.

143. Eigenmann PA, Sicherer SH, Borkowski TA, *et al.* Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics in Review* 1998;101(3):E8.

144. Hill DJ, Hosking CS. Food allergy and atopic dermatitis in infancy: An epidemiologic study. *Pediatric Allergy and Immunology* 2004;15(5):421–7.

145. Wuthrich B, Schmid-Grendelmeier P. Natural course of AEDS. *Allergy* 2002;57(3):267–8.
146. Wang IJ, Lin YT, Yang YH, *et al.* Correlation between age and allergens in pediatric atopic dermatitis. *Annals of Allergy, Asthma, and Immunology* 2004;93(4):334–8.
147. Johnke H. Patterns of sensitization in infants and its relation to atopic dermatitis. *Pediatric Allergy and Immunology* 2006;17(8):591–600.
148. Wolkerstorfer A, Wahn U, Kjellman NI, *et al.* Natural course of sensitization to cow's milk and hen's egg in childhood atopic dermatitis: ETAC study group. *Clinical and Experimental Allergy* 2002;32(1):70–3.
149. Bohme M, Svensson A, Kull I, *et al.* Clinical features of atopic dermatitis at two years of age: a prospective, population-based case–control study. *Acta Dermato-Venereologica* 2001;81(3):193–7.
150. Vicencio JCA, Gonzalez-Andaya AM. Sensitization to food and aeroallergens in children with atopic dermatitis seen at the University of Santo Tomas Hospital Allergy Clinic. *Santo Tomas Journal of Medicine* 2005;52(3):92–100.
151. Erwin EA, Platts-Mills TAE. Aeroallergens. In: Bieber T, Leung DYM, eds. *Atopic Dermatitis*. New York: Dekker; 2002. p. 357–74.
152. Ellman-Grunther L, Sampson HA. Atopic dermatitis and foods. In: Bieber T, Leung DYM, eds. *Atopic Dermatitis*. New York: Dekker; 2002. p. 375–400.
153. Darsow UG, Ring J. Allergy diagnosis in atopic eczema with the atopy patch test. In: Bieber T, Leung DYM, eds. *Atopic Dermatitis*. New York: Dekker; 2002. p. 437–51.
154. Kolmer H, Platts-Mills TA. The role of inhalant allergens in atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis: the Epidemiology, Causes and Prevention of Atopic Eczema*. Cambridge: Cambridge University Press; 2000. p. 183–92.
155. David TJ, Patel L, Ewing CI, Stanton RHJ. Dietary factors in established atopic dermatitis. In: Williams H.C, ed. *Atopic Dermatitis: the Epidemiology, Causes and Prevention of Atopic Eczema.* Cambridge: Cambridge University Press; 2000. p. 193–201.
156. Langan SM, Williams HC. What causes worsening of eczema? A systematic review. *British Journal of Dermatology* 2006;155(3):504–14.
157. Leung DY, Boguniewicz M. Advances in allergic skin diseases. *Journal of Allergy and Clinical Immunology* 2003; 111(3 Suppl):S805–12.
158. Bardana EJ Jr. Immunoglobulin E- (IgE) and non-IgE-mediated reactions in the pathogenesis of atopic eczema/dermatitis syndrome (AEDS). *Allergy* 2004;59(Suppl 78):25–9.
159. Morren MA, Przybilla B, Bamelis M, *et al.* Atopic dermatitis: triggering factors. *Journal of the American Academy of Dermatology* 1994;31(3 Pt 1):467–73.
160. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, *et al.* Standardization of food challenges in patients with immediate reactions to foods – position paper from the European Academy of Allergology and Clinical Immunology. *Allergy* 2004;59(7):690–7.
161. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *The Journal of Allergy and Clinical Immunology* 1996;97(1 Pt 1):9–15.
162. Majamaa H, Moisio P, Holm K, *et al.* Wheat allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy* 1999;54(8):851–6.
163. Niggemann B, Reibel S, Wahn U. The atopy patch test (APT) – a useful tool for the diagnosis of food allergy in children with atopic dermatitis. *Allergy* 2000;55(3):281–5.
164. Niggemann B. Atopy Patch Test (APT) – its role in diagnosis of food allergy in atopic dermatitis. *Indian Journal of Pediatrics* 2002;69(1):57–9.
165. Roehr CC, Reibel S, Ziegert M, *et al.* Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *Journal of Allergy and Clinical Immunology* 2001;107(3):548–53.
166. Niggemann B, Sielaff B, Beyer K, *et al.* Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clinical and Experimental Allergy* 1999;29(1):91–6.
167. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *The Journal of Allergy and Clinical Immunology* 1997;100(4):444–51.
168. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *The Journal of Allergy and Clinical Immunology* 1984;74(1):26–33.
169. Breuer K, Heratizadeh A, Wulf A, *et al.* Late eczematous reactions to food in children with atopic dermatitis. *Clinical and Experimental Allergy* 2004;34(5):817–24.
170. Van Bever HP, Docx M, Stevens WJ. Food and food additives in severe atopic dermatitis. *Allergy* 1989;44(8):588–94.
171. Cudowska B, Kaczmarski M. Atopy patch test in the diagnosis of food allergy in children with atopic eczema dermatitis syndrome. *Roczniki Akademii Medycznej W Bialymstoku* 2005; 50:261–7.
172. Cantani A, Arcese G, Serra A, *et al.* Results of skin tests, RAST, and food challenges in children with atopic dermatitis associated with food allergy. *Padiatrie und Padologie* 1995;30(6):113–17.
173. de Waard-van der Spek FB, Elst EF, Mulder PG, *et al.* Diagnostic tests in children with atopic dermatitis and food allergy. *Allergy* 1998;53(11):1087–91.
174. Giusti F, Seidenari S. Patch testing with egg represents a useful integration to diagnosis of egg allergy in children with atopic dermatitis. *Pediatric Dermatology* 2005;22(2):109–11.
175. Monti G, Muratore MC, Peltran A, *et al.* High incidence of adverse reactions to egg challenge on first known exposure in young atopic dermatitis children: predictive value of skin prick test and radioallergosorbent test to egg proteins. *Clinical and Experimental Allergy* 2002;32(10):1515–19.
176. Seidenari S, Giusti F, Bertoni L, *et al.* Combined skin prick and patch testing enhances identification of peanut-allergic patients with atopic dermatitis. *Allergy* 2003;58(6):495–9.
177. Stromberg L. Diagnostic accuracy of the atopy patch test and the skin-prick test for the diagnosis of food allergy in young children with atopic eczema/dermatitis syndrome. *Acta Paediatrica* 2002;91(10):1044–9.
178. Jarvinen K-M, Turpeinen M, Suomalainen H. Concurrent cereal allergy in children with cow's milk allergy manifested with atopic dermatitis. *Clinical and Experimental Allergy* 2003;33(8):1060–6.
179. Cantani A, Micera M. The prick by prick test is safe and reliable in 58 children with atopic dermatitis and food allergy. *European Review for Medical and Pharmacological Sciences* 2006;10(3):115–20.
180. Varjonen E, Vainio E, Kalimo K, *et al.* Skin-prick test and RAST responses to cereals in children with atopic dermatitis. Characterization of IgE-binding components in wheat and oats by an immunoblotting method. *Clinical and Experimental Allergy* 1995;25(11):1100–7.
181. Mehl A. The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. *Journal of Allergy and Clinical Immunology* 2006;118(4):923–9.

182. Niggemann B, Ziegert M, Reibel S. Importance of chamber size for the outcome of atopy patch testing in children with atopic dermatitis and food allergy. *The Journal of Allergy and Clinical Immunology* 2002;110(3):515–16.

183. Darsow U, Vieluf D, Ring J. Atopy patch test with different vehicles and allergen concentrations: an approach to standardization. *Journal of Allergy and Clinical Immunology* 1995;95(3):677–84.

184. Verstege A, Mehl A, Rolinck-Werninghaus C, *et al.* The predictive value of the skin prick test weal size for the outcome of oral food challenges. *Clinical and Experimental Allergy : Journal of the British Society for Allergy and Clinical Immunology* 2005;35(9):1220–6.

185. Heine RG, Verstege A, Mehl A, *et al.* Proposal for a standardized interpretation of the atopy patch test in children with atopic dermatitis and suspected food allergy. *Pediatric Allergy and Immunology* 2006;17(3):213–17.

186. Hosking CS, Heine RG, Hill DJ. The Melbourne milk allergy study – Two decades of clinical research. *Allergy and Clinical Immunology International* 2000;12(5):198–205.

187. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clinical and Experimental Allergy* 2000;30(11):1540–6.

188. Perackis K, Staden U, Mehl A, *et al.* Skin prick test with hen's egg: Whole egg or egg white? *Allergy* 2004;59(11):1236–7.

189. Kim TE, Park SW, Noh G, *et al.* Comparison of skin prick test results between crude allergen extracts from foods and commercial allergen extracts in atopic dermatitis by double-blind placebo-controlled food challenge for milk, egg, and soybean. *Yonsei Medical Journal* 2002;43(5):613–20.

190. Fiocchi A, Bouygue GR, Restani P, *et al.* Accuracy of skin prick tests in IgE-mediated adverse reactions to bovine proteins. *Annals of Allergy, Asthma and Immunology: Official Publication of the American College of Allergy, Asthma, and Immunology* 2002;89(6 Suppl 1):26–32.

191. Mehl A, Verstege A, Staden U, *et al.* Utility of the ratio of food-specific IgE/total IgE in predicting symptomatic food allergy in children. *Allergy* 2005;60(8):1034–9.

192. Fiocchi A, Bouygue GR, Martelli A, *et al.* Dietary treatment of childhood atopic eczema/dermatitis syndrome (AEDS). *Allergy* 2004; 59(Suppl 78):78–85.

193. Atherton DJ, Sewell M, Soothill JF, *et al.* A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet* 1978;1(8061):401–3.

194. Neild VS, Marsden RA, Bailes JA, *et al.* Egg and milk exclusion diets in atopic eczema. *British Journal of Dermatology* 1986;114(1):117–23.

195. Businco L, Businco E, Cantani A, *et al.* Results of a milk and/or egg free diet in children with atopic dermatitis. *Allergologia et Immunopathologia* 1982;10(4):283–8.

196. Sloper KS, Wadsworth J, Brostoff J. Children with atopic eczema. I: Clinical response to food elimination and subsequent double-blind food challenge. *Quarterly Journal of Medicine* 1991;80(292):677–93.

197. Flinterman AE, Knulst AC, Meijer. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. *Allergy* 2006;61(3):370–4.

198. Lever R, MacDonald C, Waugh P, *et al.* Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatric Allergy and Immunology* 1998;9(1):13–19.

199. Aoki T, Kojima M, Adachi J, *et al.* Effect of short-term egg exclusion diet on infantile atopic dermatitis and its relation to egg allergy: a single-blind test. *Acta Dermato-Venereologica. Supplementum* 1992;176:99–102.

200. Niggemann B, Binder C, Dupont C, *et al.* Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis. *Pediatric Allergy and Immunology* 2001;12(2):78–82.

201. Isolauri E, Sutas Y, Makinen-Kiljunen S, *et al.* Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy. *Journal of Pediatrics* 1995;127(4):550–7.

202. Cant AJ, Bailes JA, Marsden RA, *et al.* Effect of maternal dietary exclusion on breast fed infants with eczema: two controlled studies. *British Medical Journal* 1986;293(6541):231–3.

203. Kramer MS. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database of Systematic Reviews* 2007;(1).

204. van Asperen PP, Lewis M, Rogers M, *et al.* Experience with an elimination diet in children with atopic dermatitis. *Clinical Allergy* 1983;13(5):479–85.

205. Agata H, Kondo N, Fukutomi O, *et al.* Effect of elimination diets on food-specific IgE antibodies and lymphocyte proliferative responses to food antigens in atopic dermatitis patients exhibiting sensitivity to food allergens. *Journal of Allergy and Clinical Immunology* 1993;91(2):668–79.

206. Broberg A, Engstrom I, Kalimo K, *et al.* Elimination diet in young children with atopic dermatitis. *Acta Dermato-Venereologica* 1992;72(5):365–9.

207. Mabin DC, Sykes AE, David TJ. Controlled trial of a few foods diet in severe atopic dermatitis. *Archives of Disease in Childhood* 1995;73(3):202–7.

208. Devlin J, David TJ, Stanton RH. Six food diet for childhood atopic dermatitis. *Acta Dermato-Venereologica* 1991;71(1):20–4.

209. Devlin J, David TJ, Stanton RH. Elemental diet for refractory atopic eczema. *Archives of Disease in Childhood* 1991;66(1):93–9.

210. David TJ. Extreme dietary measures in the management of atopic dermatitis in childhood. *Acta Dermato-Venereologica. Supplementum* 1992;176:113–16.

211. Pike MG, Carter CM, Boulton P, *et al.* Few food diets in the treatment of atopic eczema. *Archives of Disease in Childhood* 1989;64(12):1691–8.

212. Leung TF, Ma KC, Cheung LT, *et al.* A randomized, single-blind and crossover study of an amino acid-based milk formula in treating young children with atopic dermatitis. *Pediatric Allergy and Immunology* 2004;15(6):558–61.

213. Hill DJ, Lynch BC. Elemental diet in the management of severe eczema in childhood. *Clinical Allergy* 1982;12(3):313–15.

214. Martino F, Bruno G, Aprigliano D, *et al.* Effectiveness of a home-made meat based formula (the Rezza-Cardi diet) as a diagnostic tool in children with food-induced atopic dermatitis. *Pediatric Allergy and Immunology* 1998;9(4):192–6.

215. Ehlers I, Worm M, Sterry W, *et al.* Sugar is not an aggravating factor in atopic dermatitis. *Acta Dermato-Venereologica* 2001;81(4):282–4.

216. Businco L, Meglio P, Amato G, *et al.* Evaluation of the efficacy of oral cromolyn sodium or an oligoantigenic diet in children with atopic dermatitis: a multicenter study of 1085 patients. *Journal of Investigational Allergology and Clinical Immunology* 1996;6(2):103–9.

217. Graham P, Hall-Smith SP, Harris JM, *et al.* A study of hypoallergenic diets and oral sodium cromoglycate in the management of atopic eczema. *British Journal of Dermatology* 1984;110(4):457–67.

218. Molkhou P, Waguet JC. Food allergy and atopic dermatitis in children: treatment with oral sodium cromoglycate. *Annals of Allergy* 1981;47(3):173–5.
219. Businco L, Benincori N, Nini G, *et al.* Double-blind crossover trial with oral sodium cromoglycate in children with atopic dermatitis due to food allergy. *Annals of Allergy* 1986;57(6):433–8.
220. Ewing CI, Gibbs ACC, Ashcroft C, *et al.* Failure of oral zinc supplementation in atopic eczema. *European Journal of Clinical Nutrition* 1991;45(10):507–10.
221. Tsoureli-Nikita E, Hercogova J, Lotti T, *et al.* Evaluation of dietary intake of vitamin E in the treatment of atopic dermatitis: a study of the clinical course and evaluation of the immunoglobulin E serum levels. *International Journal of Dermatology* 2002;41(3):146–50.
222. Viljanen M, Savilahti E, Haahtela T, *et al.* Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. *Allergy* 2005;60(4):494–500.
223. Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. *Journal of Allergy and Clinical Immunology* 1997;99(2):179–85.
224. Brouwer ML, Wolt-Plompen SA, Dubois AE, *et al.* No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial. *Clinical and Experimental Allergy* 2006;36(7):899–906.
225. Nishioka K, Yasueda H, Saito H. Preventive effect of bedding encasement with microfine fibers on mite sensitization. *Journal of Allergy and Clinical Immunology* 1998;101(1 Pt 1):28–32.
226. Ricci G, Patrizi A, Specchia F, *et al.* Effect of house dust mite avoidance measures in children with atopic dermatitis. *British Journal of Dermatology* 2000;143(2):379–84.
227. Tan BB, Weald D, Strickland I, *et al.* Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996;347(8993):15–18.
228. Sanda T, Yasue T, Oohashi M, *et al.* Effectiveness of house dust-mite allergen avoidance through clean room therapy in patients with atopic dermatitis. *Journal of Allergy and Clinical Immunology* 1992;89(3):653–7.
229. Glover MT, Atherton DJ. A double-blind controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with atopic eczema. *Clinical and Experimental Allergy* 1992;22(4):440–6.
230. Galli E, Chini L, Nardi S, *et al.* Use of a specific oral hyposensitization therapy to *Dermatophagoides pteronyssinus* in children with atopic dermatitis. *Allergologia et Immunopathologia* 1994;22(1):18–22.
231. Palmer CN, Irvine AD, Terron-Kwiatkowski A, *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nature Genetics* 2006;38(4):441–6.
232. BNF for Children [online] 2007 [bnfc.org/bnfc/bnfc/current/index.htm].
233. Loden M. Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. *American Journal of Clinical Dermatology* 2003;4(11):771–88.
234. Thestrup-Pedersen K. Treatment principles of atopic dermatitis. *Journal of the European Academy of Dermatology and Venereology* 2002;16(1):1–9.
235. Giordano-Labadie F. Evaluation of a new moisturizer (Exomega milk) in children with atopic dermatitis. *The Journal of Dermatological Treatment* 2006;17(2):78–81.
236. Cork MJ, Timmins J, Holden C, *et al.* An audit of adverse drug reactions to aqueous cream in children with atopic eczema. *Pharmaceutical Journal* 2003;271(7277):747–8.
237. Hindson TC. Urea in the topical treatment of atopic eczema. *Archives of Dermatology* 1971;104(3):284–5.
238. Clinical Research Group for Urea Ointment. A double-blind study on clinical efficacy of urea ointment. *Rinsho Hyoka (Clinical Evaluation)* 1977;5(1):103–25.
239. Freitag G, Hoppner T. Results of a postmarketing drug monitoring survey with a polidocanolurea preparation for dry, itching skin. *Current Medical Research and Opinion* 1997;13(9):529–37.
240. Whitefield M. Effectiveness of a new antimicrobial emollient in the management of eczema/dermatitis. *Journal of Dermatological Treatment* 1998;9(2):103–9.
241. Harper J. Double-blind comparison of an antiseptic oil-based bath additive (Oilatum Plus) with regular Oilatum (Oilatum Emollient) for the treatment of atopic eczema. *Round Table Series – Royal Society of Medicine* 1995;(37)42–7.
242. Bettzuege-Pfaff BI, Melzer A. Treating dry skin and pruritus with a bath oil containing soya oil and lauromacrogols. *Current Medical Research and Opinion* 2005;21(11):1735–9.
243. Ling TC, Highet AS. Irritant reactions to an antiseptic bath emollient. *Journal of Dermatological Treatment* 2000;11(4):263–7.
244. White MI, Batten TL, Ormerod AD. Adverse effects of a daily bathing routine on children with atopic dermatitis. *Journal of Dermatological Treatment* 1994;5(1):21–3.
245. Lucky AW, Leach AD, Laskarzewski P, *et al.* Use of an emollient as a steroid-sparing agent in the treatment of mild to moderate atopic dermatitis in children. *Pediatric Dermatology* 1997;14(4):321–4.
246. Muzaffar F, Hussain I, Rani Z, *et al.* Emollients as an adjunct therapy to topical corticosteroids in children with mild to moderate atopic dermatitis. *Journal of Pakistan Association of Dermatologists* 2002;12:64–8.
247. Cork MJ. *Complete Emollient Therapy. The National Association of Fundholding Practice Official Yearbook*. London: Scorpio; 1998. p. 159–68.
248. Grimalt R, Mengeaud V, Cambazard F, *et al.* The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: a randomized controlled study. *Dermatology* 2007;214(1):61–7.
249. Hindley D, Galloway G, Murray J, *et al.* A randomised study of "wet wraps" versus conventional treatment for atopic eczema. *Archives of Disease in Childhood* 2006;91(2):164–8.
250. Schnopp C, Holtmann C, Stock S, *et al.* Topical steroids under wet-wrap dressings in atopic dermatitis – a vehicle-controlled trial. *Dermatology* 2002;204(1):56–9.
251. Barry BW, Woodford R. Comparative bio-availability and activity of proprietary topical corticosteroid preparations: vasoconstrictor assays on thirty-one ointments. *British Journal of Dermatology* 1975;93(5):563–71.
252. Activity and bioavailabilty of topical steroids. *In vivo/in vitro* correlations for the vasoconstrictor test. *Journal of Clinical Pharmacy* 1978;3(1):43–65.
253. Long CC, Finlay AY. The finger-tip unit – a new practical measure. *Clinical and Experimental Dermatology* 1991;16(6):444–7.
254. Thomas KS, Armstrong S, Avery A, *et al.* Randomised controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild or moderate atopic eczema. *British Medical Journal* 2002;324(7340):768.

255. Kirkup ME, Birchall NM, Weinberg EG, *et al.* Acute and maintenance treatment of atopic dermatitis in children – two comparative studies with fluticasone propionate (0.05%) cream. *Journal of Dermatological Treatment* 2003;14(3):141–8.

256. Lebwohl M. A comparison of once-daily application of mometasone furoate 0.1% cream compared with twice-daily hydrocortisone valerate 0.2% cream in pediatric atopic dermatitis patients who failed to respond to hydrocortisone: mometasone furoate study group. *International Journal of Dermatology* 1999;38(8):604–6.

257. Smitt JHS, Winterberg DH, Oosting J. Treatment of atopic dermatitis with topical corticosteroids in children. Efficacy and systemic effects of triamcinolone acetonide and alclometasone dipropionate. *European Journal of Dermatology* 1993;3(7):549–52.

258. Veien NK, Hattel T, Justesen O, *et al.* Hydrocortisone 17-butyrate (Locoid) 0.1% cream versus hydrocortisone (Uniderm) 1% cream in the treatment of children suffering from atopic dermatitis. *Journal of International Medical Research* 1984;12(5):310–13.

259. Rafanelli A. Mometasone furoate in the treatment of atopic dermatitis in children. *Journal of the European Academy of Dermatology and Venereology* 1993;2(3):225–30.

260. Vernon HJ, Lane AT, Weston W. Comparison of mometasone furoate 0.1% cream and hydrocortisone 1.0% cream in the treatment of childhood atopic dermatitis. *Journal of the American Academy of Dermatology* 1991;24(4):603–7.

261. Wolkerstorfer A, Strobos MA, Glazenburg EJ, *et al.* Fluticasone propionate 0.05% cream once daily versus clobetasone butyrate 0.05% cream twice daily in children with atopic dermatitis. *Journal of the American Academy of Dermatology* 1998;39(2 Pt 1):226–31.

262. Lassus A. Clinical comparison of alclometasone dipropionate cream 0.05% with hydrocortisone butyrate cream 0.1% in the treatment of atopic dermatitis in children. *Journal of International Medical Research* 1983;11(5):315–19.

263. Lassus A. Alclometasone dipropionate cream 0.05% versus clobetasone butyrate cream 0.05%. A controlled clinical comparison in the treatment of atopic dermatitis in children. *International Journal of Dermatology* 1984;23(8):565–6.

264. Munkvad M. A comparative trial of Clinitar versus hydrocortisone cream in the treatment of atopic eczema. *British Journal of Dermatology* 1989;121(6):763–6.

265. Reitamo S, Harper J, Dbos J, *et al.* 0.03% Tacrolimus ointment applied once or twice daily is more efficacious than 1% hydrocortisone acetate in children with moderate to severe atopic dermatitis: Results of a randomized double-blind controlled trial. *British Journal of Dermatology* 2004;150(3):554–62.

266. Reitamo S, Van Leent EJ, Ho V, *et al.* Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. *The Journal of Allergy and Clinical Immunology* 2002;109(3):539–46.

267. Sikder M, Al Mamun S., Khan RM, *et al.* Topical 0.03% tacrolimus ointment, 0.05% clobetasone butyrate cream alone and their combination in older children with atopic dermatitis – An open randomized comparative study. *Journal of Pakistan Association of Dermatologists* 2005;15(4):304–12.

268. Andersen BL, Andersen KE, Nielsen R, *et al.* Treatment of dry atopic dermatitis in children. A double-blind comparison between Mildison lipocream(TM) (1% hydrocortisone) and Uniderm(TM) (1% hydrocortisone) ointment. *Clinical Trials Journal* 1988;25(4):278–84.

269. Olholm Larsen P, Brandrup F, Roders GA. Report on a double-blind, left-right study comparing the clinical efficacy of Mildison (hydrocortisone 1%) Lipocream(TM) with Uniderm(TM) (hydrocortisone 1%) cream in the treatment of children with atopic dermatitis. *Current Therapeutic Research* 1988;44(3):421–5.

270. Stalder JF, Fleury M, Sourisse M, *et al.* Local steroid therapy and bacterial skin flora in atopic dermatitis. *British Journal of Dermatology* 1994;131(4):536–40.

271. Roth HL, Brown EP. Hydrocortisone valerate. Double-blind comparison with two other topical steroids. *Cutis* 1978;21(5):695–8.

272. Hanifin JM, Hebert AA, Mays SR, *et al.* Effects of a low-potency corticosteroid lotion plus a moisturizing regimen in the treatment of atopic dermatitis. *Current Therapeutic Research* 1998;59(4):227–33.

273. Lupton ES, Abbrecht MM, Brandon ML. Short-term topical corticosteroid therapy (halcinonide ointment) in the management of atopic dermatitis. *Cutis* 1982;30(5):671–5.

274. Boner AL, Richelli C, De SG, *et al.* Hypothalamic–pituitary–adrenal function in children with atopic dermatitis treated with clobetasone butyrate and its clinical evaluation. *International Journal of Clinical Pharmacology, Therapy, and Toxicology* 1985;23(2):118–20.

275. Boner AL, Richelli C, De SG, *et al.* Adrenocortical function during prolonged treatment with clobetasone butyrate in children with chronic atopic dermatitis and elevated IgE levels. *International Journal of Clinical Pharmacology Research* 1985;5(2):127–31.

276. Friedlander SF, Hebert AA, Allen DB, *et al.* Safety of fluticasone propionate cream 0.05% for the treatment of severe and extensive atopic dermatitis in children as young as 3 months. *Journal of the American Academy of Dermatology* 2002;46(3):387–93.

277. Queille C, Pommarede R, Saurat JH. Efficacy versus systemic effects of six topical steroids in the treatment of atopic dermatitis of childhood. *Pediatric Dermatology* 1984;1(3):246–53.

278. Patel L, Clayton PE, Addison GM, *et al.* Adrenal function following topical steroid treatment in children with atopic dermatitis. *British Journal of Dermatology* 1995;132(6):950–5.

279. Ellison JA, Patel L, Ray DW, *et al.* Hypothalamic-pituitary-adrenal function and glucocorticoid sensitivity in atopic dermatitis. *Pediatrics* 2000;105(4 Part 1):794–9.

280. Furue M, Terao H, Rikihisa W, *et al.* Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis. *British Journal of Dermatology* 2003;148(1):128–33.

281. Hengge UR, Ruzicka T, Schwartz RA, *et al.* Adverse effects of topical glucocorticosteroids. *Journal of the American Academy of Dermatology* 2006;54(1):1–18.

282. Callen J, Chamlin S, Eichenfield LF, *et al.* A systematic review of the safety of topical therapies for atopic dermatitis. *British Journal of Dermatology* 2007;156(2):203–21.

283. Sefton J, Galen WK, Nesbitt LT, *et al.* Comparative efficacy of hydrocortisone valerate 0.2% cream and triamcinolone acetonide 0.1% cream in the treatment of atopic dermatitis. *Current Therapeutic Research, Clinical and Experimental* 1983;34(2 Pat 1):341–4.

284. Prado de Oliveira ZN, Cuce LC, Arnone M. Comparative evaluation of efficacy, tolerability and safety of 0.1% topical momethasone furoate and 0.05% desonide in the treatment of childhood atopic dermatitis. *Anais Brasileiros de Dermatologia* 2002;77(1):25–33.

285. Lucky AW, Grote GD, Williams JL, *et al.* Effect of desonide ointment, 0.05%, on the hypothalamic-pituitary-adrenal axis of children with atopic dermatitis. *Cutis* 1997;59(3):151–3.

286. Bleehen SS, Chu AC, Hamann I, *et al.* Fluticasone propionate 0.05% cream in the treatment of atopic eczema: a multicentre study comparing once-daily treatment and once-daily vehicle cream application versus twice-daily treatment. *British Journal of Dermatology* 1995;133(4):592–7.

287. Richelli C, Piacentini GL, Sette L, *et al.* Clinical efficacy and tolerability of clobetasone 17-butyrate 0.5% lotion in children with atopic dermatitis. *Current Therapeutic Research* 1990;47(3):413–17.

288. Green C, Colquitt JL, Kirby J, Davidson P, Payne E. Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation. *Health Technology Assessment* 2004;8(47): iii,iv,1–120.

289. Hebert AA, Friedlander SF, Allen DB. Topical fluticasone propionate lotion does not cause HPA axis suppression. *Journal of Pediatrics* 2006;149(3):378–82.

290. Hebert AA, Friedlander SF, Allen DB. Topical fluticasone propionate lotion does not cause HPA axis suppression. *Journal of Pediatrics* 2006;149(3):378–82.

291. Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, Payne L. The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation. *Health Technology Assessment* 2005;9(29):iii,xi–xiii,1–230.

292. Boguniewicz M, Fiedler VC, Raimer S, *et al.* A randomized, vehicle-controlled trial of tacrolimus ointment for treatment of atopic dermatitis in children. Pediatric Tacrolimus Study Group. *Journal of Allergy and Clinical Immunology* 1998;102(4 Pt 1):637–44.

293. Paller A, Eichenfield LF, Leung DY, *et al.* A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. *Journal of the American Academy of Dermatology* 2001;44(1 Suppl):S47-57.

294. Drake L, Prendergast M, Maher R, *et al.* The impact of tacrolimus ointment on health-related quality of life of adult and pediatric patients with atopic dermatitis. *Journal of the American Academy of Dermatology* 2001;44(1 Suppl):S65-72.

295. Eichenfield LF, Lucky AW, Boguniewicz M, *et al.* Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. *Journal of the American Academy of Dermatology* 2002;46(4):495–504.

296. Whalley D, Huels J, McKenna SP, *et al.* The benefit of pimecrolimus (Elidel, SDZ ASM 981) on parents' quality of life in the treatment of pediatric atopic dermatitis. *Pediatrics* 2002;110(6):1133–6.

297. Wahn U, Bos JD, Goodfield M, *et al.* Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. *Pediatrics* 2002;110(1 Pt 1):e2.

298. Ashcroft DM, Dimmock P, Garside R, *et al.* Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *British Medical Journal* 2005;330:(7490):516.

299. Ho VC, Gupta A, Kaufmann R, *et al.* Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. *Journal of Pediatrics* 2003;142(2):155–62.

300. Breuer K, Braeutigam M, Kapp A, *et al.* Influence of pimecrolimus cream 1% on different morphological signs of eczema in infants with atopic dermatitis. *Dermatology* 2004;209(4):314–20.

301. Kaufmann R, Folster-Holst R, Hoger P, *et al.* Onset of action of pimecrolimus cream 1% in the treatment of atopic eczema in infants. *Journal of Allergy and Clinical Immunology* 2004;114(5):1183–8.

302. Kapp A, Papp K, Bingham A, *et al.* Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. *Journal of Allergy and Clinical Immunology* 2002;110(2):277–84.

303. Papp KA, Werfel T, Folster-Holst R, *et al.* Long-term control of atopic dermatitis with pimecrolimus cream 1% in infants and young children: a two-year study. *Journal of the American Academy of Dermatology* 2005;52(2):240–6.

304. Siegfried E, Korman N, Molina C, *et al.* Safety and efficacy of early intervention with pimecrolimus cream 1% combined with corticosteroids for major flares in infants and children with atopic dermatitis. *Journal of Dermatological Treatment* 2006;17(3):143–50.

305. Kempers S, Boguniewicz M, Carter E, *et al.* A randomized investigator-blinded study comparing pimecrolimus cream 1% with tacrolimus ointment 0.03% in the treatment of pediatric patients with moderate atopic dermatitis. *Journal of the American Academy of Dermatology* 2004;51(4):515–25.

306. Eichenfield LF, Lucky AW, Langley RG, *et al.* Use of pimecrolimus cream 1% (Elidel) in the treatment of atopic dermatitis in infants and children: the effects of ethnic origin and baseline disease severity on treatment outcome. *International Journal of Dermatology* 2005;44(1):70–5.

307. Schachner LA, Lamerson C, Sheehan MP, *et al.* Tacrolimus ointment 0.03% is safe and effective for the treatment of mild to moderate atopic dermatitis in pediatric patients: results from a randomized, double-blind, vehicle-controlled study. *Pediatrics* 2005;116(3):e334–42.

308. Bieber T. Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.03% in children and adolescents with an acute flare of severe atopic dermatitis. *Allergy* 2007;62(2):184–9.

309. Arkwright PD, Gillespie MC, Ewing CI, *et al.* Blinded side-to-side comparison of topical corticosteroid and tacrolimus ointment in children with moderate to severe atopic dermatitis. *Clinical and Experimental Dermatology* 2007;32(2):145–7.

310. Koo JYM, Fleischer Jr AB, Abramovits W, *et al.* Tacrolimus ointment is safe and effective in the treatment of atopic dermatitis: Results in 8000 patients. *Journal of the American Academy of Dermatology* 2005;53(2 Suppl 2):S195–205.

311. Tan J, Langley R. Safety and efficacy of tacrolimus ointment 0.1% (Protopic) in atopic dermatitis: a Canadian open-label multicenter study. *Journal of Cutaneous Medicine and Surgery* 2004;8(4):213–19.

312. Hanifin JM, Paller AS, Eichenfield L, *et al.* Efficacy and safety of tacrolimus ointment treatment for up to 4 years in patients with atopic dermatitis. *Journal of the American Academy of Dermatology* 2005;53(2 Suppl 2):S186–94.

313. Remitz A. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. *Acta Dermato-Venereologica* 2007;87(1):54–61.

314. Singalavanija S, Noppakun. Efficacy and safety of tacrolimus ointment in pediatric Patients with moderate to severe atopic dermatitis. *Journal of the Medical Association of Thailand* 2006;89(11):1915–22.

315. Lubbe J, Friedlander SF, Cribier B, *et al.* Safety, efficacy, and dosage of 1% pimecrolimus cream for the treatment of atopic dermatitis in daily practice. *American Journal of Clinical Dermatology* 2006;7(2):121–31.

316. Staab D, Pariser D, Gottlieb AB, *et al.* Low systemic absorption and good tolerability of pimecrolimus, administered as 1% cream (Elidel) in infants with atopic dermatitis--a multicenter, 3-week, open-label study. *Pediatric Dermatology* 2005;22(5):465–71.

317. Allen BR, Lakhanpaul M, Morris A, *et al.* Systemic exposure, tolerability, and efficacy of pimecrolimus cream 1% in atopic dermatitis patients. *Archives of Disease in Childhood* 2003;88(11):969–73.

318. Lakhanpaul M, Davies T, Allen BR, *et al.* Low systemic exposure in infants with atopic dermatitis in a 1-year pharmacokinetic study with pimecrolimus cream 1%. *Experimental Dermatology* 2006;15(2):138–41.

319. Topical tacrolimus (Protopic) and pimecrolimus (Elidel): reports of malignancies. *Current Problems in Pharmacovigilance* 2006;31:1–2.

320. Ellis CN, Kahler KH, Grueger J, *et al.* Cost effectiveness of management of mild-to-moderate atopic dermatitis with 1% pimecrolimus cream in children and adolescents 2–17 years of age. *American Journal of Clinical Dermatology* 2006;7(2):133–9.

321. Pitt M, Garside R, Stein K. A cost-utility analysis of pimecrolimus vs. topical corticosteroids and emollients for the treatment of mild and moderate atopic eczema. *British Journal of Dermatology* 2006;154(6):1137–46.

322. Coyle D, Barbeau M. Cost effectiveness of elidel in the management of patients with atopic dermatitis in Canada. *Journal of Cutaneous Medicine and Surgery* 2004;8(6):405–10.

323. Goodyear HM, Harper JI. 'Wet wrap' dressings for eczema: an effective treatment but not to be misused. *British Journal of Dermatology* 2002;146(1):159.

324. Devillers ACA, Oranje AP. Efficacy and safety of 'wet-wrap' dressings as an intervention treatment in children with severe and/or refractory atopic dermatitis: A critical review of the literature. *British Journal of Dermatology* 2006;154(4):579–85.

325. Oranje A, Devillers A, Kunz B, *et al.* Treatment of patients with atopic dermatitis using wet-wrap dressings with diluted steroids and/or emollients. An expert panel's opinion and review of the literature. *Journal of the European Academy of Dermatology and Venereology* 2006;20(10):1277–86.

326. Beattie PE, Lewis-Jones MS. A pilot study on the use of wet wraps in infants with moderate atopic eczema. *Clinical and Experimental Dermatology* 2004;29(4):348–53.

327. Pei AYS, Chan HHL, Ho KM. The effectiveness of wet wrap dressings using 0.1% mometasone furoate and 0.005% fluticasone proprionate ointments in the treatment of moderate to severe atopic dermatitis in children. *Pediatric Dermatology* 2001;18(4):343–8.

328. Wolkerstorfer A, Visser RL, De Waard van der Spek FB, *et al.* Efficacy and safety of wet-wrap dressings in children with severe atopic dermatitis: influence of corticosteroid dilution. *British Journal of Dermatology* 2000;143(5):999–1004.

329. Devillers ACA, de Waard-van der Spek FB, Mulder PGH, *et al.* Treatment of refractory atopic dermatitis using 'wet-wrap' dressings and diluted corticosteroids: Results of standardized treatment in both children and adults. *Dermatology* 2002;204(1):50–5.

330. Tang WYM, Chan HHL, Lam VMF, *et al.* Outpatient, short-term, once-daily, diluted, 0.1% mometasone furoate wet-wraps for childhood atopic eczema. *Journal of Dermatological Treatment* 1999;10(3):157–63.

331. McGowan R, Tucker P, Joseph D, *et al.* Short-term growth and bone turnover in children undergoing occlusive steroid ('Wet-Wrap') dressings for treatment of atopic eczema. *Journal of Dermatological Treatment* 2003;14(3):149–52.

332. Oranje AP, Wolkerstorfer A, De Waard-Van Der Spek FB. Treatment of erythrodermic atopic dermatitis with 'wet-wrap' fluticasone propionate 0.05% cream/emollient 1:1 dressings. *Journal of Dermatological Treatment* 1999;10(1):73–4.

333. Volden G. Successful treatment of therapy-resistant atopic dermatitis with clobetasol propionate and a hydrocolloid occlusive dressing. *Acta Dermato-Venereologica. Supplementum* 1992;176:126–8.

334. Goodyear HM, Spowart K, Harper JI. 'Wet-wrap' dressings for the treatment of atopic eczema in children. *British Journal of Dermatology* 1991;125(6):604.

335. Niordson AM, Stahl D. Treatment of psoriasis with Clinitar Cream. A controlled clinical trial. *British Journal of Clinical Practice* 1985;39(2):67–8,72.

336. Stainer R, Matthews S, Arshad SH, *et al.* Efficacy and acceptability of a new topical skin lotion of sodium cromoglicate (Altoderm) in atopic dermatitis in children aged 2–12 years: A double-blind, randomized, placebo-controlled trial. *British Journal of Dermatology.* 2005;152(2):334–41.

337. Moore C, Ehlayel MS, Junprasert J, *et al.* Topical sodium cromoglycate in the treatment of moderate-to-severe atopic dermatitis. *Annals of Allergy, Asthma, and Immunology* 1998;81(5 Pt 1):452–8.

338. La Rosa M, Ranno C, Musarra I, *et al.* Double-blind study of cetirizine in atopic eczema in children. *Annals of Allergy* 1994;73(2):117–22.

339. Munday J, Bloomfield R, Goldman M, *et al.* Chlorpheniramine is no more effective than placebo in relieving the symptoms of childhood atopic dermatitis with a nocturnal itching and scratching component. *Dermatology* 2002;205(1):40–5.

340. Klein GL, Galant SP. A comparison of the antipruritic efficacy of hydroxyzine and cyproheptadine in children with atopic dermatitis. *Annals of Allergy* 1980;44(3):142–5.

341. Yoshida H, Niimura M, Ueda H, *et al.* Clinical evaluation of ketotifen syrup on atopic dermatitis: a comparative multicenter double-blind study of ketotifen and clemastine. *Annals of Allergy* 1989;62(6):507–12.

342. Chunharas A, Wisuthsarewong W, Wananukul S, *et al.* Therapeutic efficacy and safety of loratadine syrup in childhood atopic dermatitis treated with mometasone furoate 0.1 per cent cream. *Journal of the Medical Association of Thailand* 2002;85(4):482–7.

343. Diepgen TL, Early Treatment of the Atopic Child Study Group. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. *Pediatric Allergy and Immunology* 2002;13(4):278–86.

344. Simons FER. Prospective, long-term safety evaluation of the H1-receptor antagonist cetirizine in very young children with atopic dermatitis. *Journal of Allergy and Clinical Immunology* 1999;104(2 Pt 1):433–40.

345. Stevenson J, Cornah D, Evrard P, *et al.* Long-term evaluation of the impact of the H1-receptor antagonist cetirizine on the behavioral, cognitive, and psychomotor development of very young children with atopic dermatitis. *Pediatric Research* 2002;52(2):251–7.

346. Estelle F, Simons R. Prevention of acute urticaria in young children with atopic dermatitis. *Journal of Allergy and Clinical Immunology* 2001;107(4):703–6.

347. Higaki S, Morimatsu. Staphylococcus species on the skin surface of infant atopic dermatitis patients. *Journal of International Medical Research* 1998;26(2):98–101.

348. Keswick BH, Seymour JL, Milligan MC. Diaper area skin microflora of normal children and children with atopic dermatitis. *Journal of Clinical Microbiology* 1987;25(2):216–21.

349. Szakos E, Lakos. Relationship between skin bacterial colonization and the occurrence of allergen-specific and non-allergen-specific antibodies in sera of children with atopic eczema/dermatitis syndrome. *Acta Dermato-Venereologica* 2004;84(1):32–6.

350. Williams RE, Gibson AG, Aitchison TC, *et al.* Assessment of a contact-plate sampling technique and subsequent quantitative bacterial studies in atopic dermatitis. *British Journal of Dermatology* 1990;123(4):493–501.

351. Arslanagic N. Atopic dermatitis and *Staphylococcus aureus*. *Medicinski Arhiv* 2004;58(6):363–5.

352. Ricci G. Frequency and clinical role of *Staphylococcus aureus* overinfection in atopic dermatitis in children. *Pediatric Dermatology* 2003;20(5):389–92.

353. Monti G. *Staphylococcus aureus* skin colonization in infants with atopic dermatitis. *Dermatology* 1996;193(2):83–7.

354. Leyden JJ, Marples RR, Kligman AM. *Staphylococcus aureus* in the lesions of atopic dermatitis. *British Journal of Dermatology* 1974;90(5):525–30.

355. Falanga V. Nasal carriage of *Staphylococcus aureus* and antistaphylococcal immunoglobulin E antibodies in atopic dermatitis. *Journal of Clinical Microbiology* 1985;22(3):452–4.

356. Hon K. Clinical features associated with nasal *Staphylococcus aureus* colonisation in Chinese children with moderate-to-severe atopic dermatitis. *Annals of the Academy of Medicine, Singapore* 2005;34(10):602–5.

357. Kyu HK, Ji HH, Kyoung CP. Periauricular eczematization in childhood atopic dermatitis. *Pediatric Dermatology* 1996;13(4):278–80.
358. Williams JV, Vowels BR, Honig PJ, *et al. S. aureus* isolation from the lesions, the hands, and the anterior nares of patients with atopic dermatitis. *Pediatric Dermatology* 1998;15(3):194–8.
359. Hoeger PH. Staphylococcal skin colonization in children with atopic dermatitis: prevalence, persistence, and transmission of toxigenic and nontoxigenic strains. *Journal of Infectious Diseases* 1992;165(6):1064–8.
360. Smith RJ, Alder VG, Warin RP. Pyogenic cocci in infantile eczema throughout one year. *British Medical Journal* 1975;3(5977):199–201.
361. Patel GK. *Staphylococcus aureus* colonization of children with atopic eczema and their parents [2]. *Acta Dermato-Venereologica* 2001;81(5):366–7.
362. Roll A. Microbial colonization and atopic dermatitis. *Current Opinion in Allergy and Clinical Immunology* 2004;4(5):373–8.
363. Lomholt H. *Staphylococcus aureus* clonal dynamics and virulence factors in children with atopic dermatitis. *Journal of Investigative Dermatology* 2005;125(5):977–82.
364. Matsui K. Comparative study of *Staphylococcus aureus* isolated from lesional and non-lesional skin of atopic dermatitis patients. *Microbiology and Immunology* 2000;44(11):945–7.
365. David TJ, Richmond SJ, Bailey AS. Serological evidence of herpes simplex virus infection in atopic eczema. *Archives of Disease in Childhood* 1987;62(4):416–17.
366. Rystedt I, Strannegard IL, Strannegard O. Recurrent viral infections in patients with past or present atopic dermatitis. *British Journal of Dermatology* 1986;114(5):575–82.
367. Verbov J. Severe varicella in a child with atopic eczema and ichthyosis. *Practitioner* 1986;230(1411):15–16.
368. Williams H. Are viral warts seen more commonly in children with eczema? *Archives of Dermatology* 1993;129(6):717–20.
369. Broberg A. *Pityrosporum ovale* in healthy children, infantile seborrhoeic dermatitis and atopic dermatitis. *Acta Dermato-Venereologica. Supplementum* 1994;191:2–47.
370. Jang K. Tinea pedis in Korean children. *International Journal of Dermatology* 2000;39(1):25–7.
371. Arzumanyan VG, Magarshak OO, Semenov BF. Yeast fungi in patients with allergic diseases: Species variety and sensitivity to antifungal drugs. *Bulletin of Experimental Biology and Medicine* 2000;129(6):601–4.
372. Ventura A. The effect of bacterial infection in the worsening of atopic dermatitis: correlations with humoral immunologic patterns. *Annals of Allergy* 1989;63(2):121–6.
373. Hanifin JM. Staphylococcal infections in patients with atopic dermatitis. *Archives of Dermatology* 1977;113(10):1383–6.
374. Hoeger PH. Staphylococcal septicemia in children with atopic dermatitis. *Pediatric Dermatology* 2000;17(2):111–14.
375. Sharma AK. Atopic dermatitis and *Staphylococcus aureus*-induced osteomyelitis – a peculiar association in a case. *Pediatric Dermatology* 1997;14(6):453–5.
376. Pike MG. Atopic dermatitis complicated by acute bacterial endocarditis. *Acta Paediatrica Scandinavica* 1989;78(3):463–4.
377. David TJ, Cambridge GC. Bacterial infection and atopic eczema. *Archives of Disease in Childhood* 1986;61(1):20–3.
378. Adachi J. Increasing incidence of streptococcal impetigo in atopic dermatitis. *Journal of Dermatological Science* 1998;17(1):45–53.
379. Higaki S, Nakamura. Secondary infections with beta-hemolytic streptococci in skin lesions. *International Journal of Tissue Reactions* 2003;25(2):47–50.
380. Adachi J. Group G streptococcal impetigo in atopic dermatitis – Case reports. *Skin Research* 1996;38(6):581–4.
381. Scheinfeld N. Superinfection of eczema with multiple Acinetobacter species [8]. *Acta Dermato-Venereologica* 2003;83(2):143.
382. Leyden JJ. Localized herpes simplex infections in atopic dermatitis. *Archives of Dermatology* 1979;115(3):311–12.
383. David TJ. Herpes simplex infections in atopic eczema. *Archives of Disease in Childhood* 1985;60(4):338–43.
384. Taieb A. Clinical epidemiology of symptomatic primary herpetic infection in children. A study of 50 cases. *Acta Paediatrica Scandinavica* 1987;76(1):128–32.
385. Novelli VM, Atherton DJ, Marshall WC. Eczema herpeticum. Clinical and laboratory features. *Clinical Pediatrics* 1988;27(5):231–3.
386. Fivenson DP, Breneman DL, Wander AH. Kaposi's varicelliform eruption. Absence of ocular involvement. *Archives of Dermatology* 1990;126(8):1037–9.
387. Lai Y. Eczema herpeticum in children with atopic dermatitis. *Acta Paediatrica Taiwanica* 1999;40(5):325–9.
388. Callen JP. Epidemic herpes simplex virus infection. *American Journal of Diseases of Children* 1983;137(2):182–4.
389. David TJ, Lakhani PK, Haeney MR. Severe atopic eczema, recurrent pneumococcal meningitis and recurrent eczema herpeticum. *Journal of the Royal Society of Medicine* 1984;77(8):696–7.
390. Cox GF, Levy ML, Wolf JE. Is eczema herpeticum associated with the use of hot tubs? *Pediatric Dermatology* 1985;2(4):322–3.
391. Muelleman PJ, Doyle JA, House RF. Eczema herpeticum treated with oral acyclovir. *Journal of the American Academy of Dermatology* 1986;15(4 Pt 1):716–17.
392. Sanderson IR, Brueton LA, Savage MO, *et al.* Eczema herpeticum: a potentially fatal disease. *British Medical Journal* 1987;294(6573):693–4.
393. Bajoghli A. Pathological case of the month. Eczema herpeticum. *Archives of Pediatrics and Adolescent Medicine* 1999;153(8):891–2.
394. Katta R. Painful skin erosions and fever in an infant. Eczema herpeticum. *Postgraduate Medicine* 2001;109(2):129–30.
395. Mackley CL, Adams DR, Anderson. Eczema herpeticum: a dermatologic emergency. *Dermatology Nursing* 2002;14(5):307–10.
396. Khan MS. Eczema herpeticum: a case report. *International Journal of Paediatric Dentistry* 2005;15(2):136–9.
397. Kubeyinje EP. Varicella infection in Saudi children with atopic eczema. *Medical Science Research* 1995;23(9):591–2.
398. Lipman BL. Atopic dermatitis in an infant complicated by generalized verrucae vulgares. *Annals of Allergy* 1983;51(1 Pt 1):33–4.
399. Kakourou T. Molluscum contagiosum in Greek children: a case series. *International Journal of Dermatology* 2005;44(3):221–3.
400. Dohil MA. The epidemiology of molluscum contagiosum in children. *Journal of the American Academy of Dermatology* 2006;54(1):47–54.
401. Solomon LM. Eruptive molluscum contagiosum in atopic dermatitis. *Canadian Medical Association Journal* 1966;95(19):978–9.
402. Keipert JA. The association of molluscum contagiosum and infantile eczema. *Medical Journal of Australia* 1971;1(5):267–70.
403. Block SH. The association of molluscum contagiosum and infantile eczema. *Medical Journal of Australia* 1972;2(11):626–7.
404. McHenry PM, Williams HC, Bingham EA. Management of atopic eczema. Joint Workshop of the British Association of Dermatologists and the Research Unit of the Royal College of Physicians of London. *British Medical Journal* 1995;310(6983):843–7.

405. Dhar S, Kanwar AJ, Kauer. Role of bacterial flora in the pathogenesis and management of atopic dermatitis. *IJMR (Indian Journal of Medical Research) Section A* 1992;95:234–8.
406. Ewing CI. Flucloxacillin in the treatment of atopic dermatitis. *British Journal of Dermatology* 1998;138(6):1022–9.
407. Boguniewicz M. Effects of cefuroxime axetil on Staphylococcus aureus colonization and superantigen production in atopic dermatitis. *The Journal of allergy and clinical immunology* 2001;108(4):651–2.
408. Stalder JE. Comparative effects of two topical antiseptics (Chlorhexidine vs KMnO4) on bacterial skin flora in atopic dermatitis. *Acta Dermato-Venereologica Supplementum* 1992;(176):132–4.
409. Breneman DL, Hanifin JM, Berge CA, *et al.* The effect of antibacterial soap with 1.5% triclocarban on *Staphylococcus aureus* in patients with atopic dermatitis. *Cutis* 2000;66(4):296–300.
410. Sasai-Takedatsu M. Reduction of *Staphylococcus aureus* in atopic skin lesions with acid electrolytic water – a new therapeutic strategy for atopic dermatitis. *Allergy* 1997;52(10):1012–16.
411. Ricci G. Evaluation of the antibacterial activity of a special silk textile in the treatment of atopic dermatitis. *Dermatology* 2006;213(3):224–7.
412. Noble WC. Steroid cream contaminated with Pseudomonas aeruginosa. *Lancet* 1966;1(7433):347–9.
413. Savin JA. Topical steroids and bacterial infection. *British Journal of Dermatology* 1976;94 Suppl 12:125–8.
414. Baird RM, Awad ZA, Shooter RA, *et al.* Contaminated medicaments in use in a hospital for diseases of the skin. *Journal of Hygiene* 1980;84(1):103–8.
415. Millar BC. Isolation of *Alternaria alternata* from an emollient cream: implications for public health. *Mycopathologia* 2003;156(4):273–7.
416. Weinberg E, Fourie B, Allmann B, Toerien A. The use of cefadroxil in superinfected atopic dermatitis. *Current Therapeutic Research, Clinical and Experimental* 1992;52(5):671–6.
417. Kimata H. Effect of nadifloxacin on atopic dermatitis with methicillin-resistant *Staphylococcus aureus* in young children. *European Journal of Pediatrics* 1999;158(11):949.
418. Luber H. Mupirocin and the eradication of *Staphylococcus aureus* in atopic dermatitis. *Archives of Dermatology* 1988;124(6):853–4.
419. Hjorth N, Schmidt H, Thomsen K. Fusidic acid plus betamethasone in infected or potentially infected eczema. *Pharmatherapeutica* 1985;4(2):126–31.
420. Goodyear HM, Watson PJ, Egan SA, *et al.* Skin microflora of atopic eczema in first time hospital attenders. *Clinical and Experimental Dermatology* 1993;18(4):300–4.
421. Goh CL, Wong JS, Giam YC. Skin colonization of *Staphylococcus aureus* in atopic dermatitis patients seen at the National Skin Centre, Singapore. *International Journal of Dermatology* 1997;36(9):653–7.
422. Shah M. High levels of fusidic acid-resistant *Staphylococcus aureus* in dermatology patients. *British Journal of Dermatology* 2003;148(5):1018–20.
423. Hoeger PH. Antimicrobial susceptibility of skin-colonizing *S. aureus* strains in children with atopic dermatitis. *Pediatric Allergy and Immunology* 2004;15(5):474–7.
424. El-Zimaity D, Kearns AM, Dawson SJ, *et al.* Survey, characterization and susceptibility to fusidic acid of *Staphylococcus aureus* in the Carmarthen area. *Journal of Antimicrobial Chemotherapy* 2004;54(2):441–6.
425. Langan SM, Thomas KS, Williams HC. What is meant by a "flare" in atopic dermatitis? *Archives of Dermatology* 2006;142(9):1190–6.
426. Ricci G, Patrizi A, Bendandi B, *et al.* Clinical effectiveness of a silk fabric in the treatment of atopic dermatitis. *British Journal of Dermatology* 2004;150(1):127–31.
427. Hanifin J, Gupta AK, Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. *British Journal of Dermatology* 2002;147(3):528–37.
428. Berth-Jones J, Damstra RJ, Golsch S, *et al.* Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *British Medical Journal* 2003;326(7403):1367.
429. Van Der Meer JB, Glazenburg EJ, Mulder PGH, *et al.* The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. *British Journal of Dermatology* 1999;140(6):1114–21.
430. Ibbotson SH, Bilsland D, Cox NH, *et al.* An update and guidance on narrowband ultraviolet B phototherapy: a British Photodermatology Group Workshop Report. *British Journal of Dermatology* 2004;151(2):283–97.
431. Tzung TY, Lin CB, Chen YH, *et al.* Pimecrolimus and narrowband UVB as monotherapy or combination therapy in children and adolescents with atopic dermatitis. *Acta Dermato-Venereologica* 2006;86(1):34–8.
432. Silva SH, Guedes AC, Gontijo B, *et al.* Influence of narrow-band UVB phototherapy on cutaneous microbiota of children with atopic dermatitis. *Journal of the European Academy of Dermatology and Venereology* 2006;20(9):1114–20.
433. Tay Y. Experience with UVB phototherapy in children. *Pediatric Dermatology* 1996;13(5):406–9.
434. Pasic A. Phototherapy in pediatric patients. *Pediatric Dermatology* 2003;20(1):71–7.
435. Jury CS. Narrowband ultraviolet B (UVB) phototherapy in children. *Clinical and Experimental Dermatology* 2006;31(2):196–9.
436. Collins P. Narrowband (TL-01) UVB air-conditioned phototherapy for atopic eczema in children. *British Journal of Dermatology* 1995;133(4):653–5.
437. Clayton TH, Clark SM, Turner. The treatment of severe atopic dermatitis in childhood with narrowband ultraviolet B phototherapy. *Clinical and Experimental Dermatology* 2007;32(1):28–33.
438. Sheehan MP, Atherton DJ, Norris P, *et al.* Oral psoralen photochemotherapy in severe childhood atopic eczema: an update. *British Journal of Dermatology* 1993;129(4):431–6.
439. Atherton DJ. The role of psoralen photochemotherapy (PUVA) in the treatment of severe atopic eczema in adolescents. *British Journal of Dermatology* 1988;118(6):791–5.
440. Harper JI. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *British Journal of Dermatology* 2000;142(1):52–8.
441. Zaki I. Treatment of severe atopic dermatitis in childhood with cyclosporin. *British Journal of Dermatology* 1996;135(Suppl 48):21–4.
442. Bunikowski R, Staab D, Kussebi F, *et al.* Low-dose cyclosporin A microemulsion in children with severe atopic dermatitis: clinical and immunological effects. *Pediatric Allergy and Immunology* 2001;12(4):216–23.
443. von Ruden U. Cyclosporin A treatment of children with severe atopic dermatitis improves quality of life of their mothers. *Dermatology and Psychosomatics* 2002;3(1):14–18.

444. Bunikowski R. Effect of low-dose cyclosporin a microemulsion on disease severity, interleukin-6, interleukin-8 and tumor necrosis factor alpha production in severe pediatric atopic dermatitis. *International Archives of Allergy and Immunology* 2001;125(4):344–8.

445. Bunikowski R. Effect of oral cyclosporin A in children with *Staphylococcus aureus*-colonized vs *S aureus*-infected severe atopic dermatitis. *Pediatric Allergy and Immunology* 2003;14(1):55–9.

446. Leonardi S, Marchese G, Rotolo N, *et al.* Cyclosporin is safe and effective in severe atopic dermatitis of childhood. Report of three cases. *Minerva Pediatrica* 2004;56(2):231–7.

447. Bourke JF. A new microemulsion formulation of cyclosporin (Neoral) is effective in the treatment of cyclosporin-resistant dermatoses. *British Journal of Dermatology* 1996;134(4):777–9.

448. Ahmed I. Paradoxical normalization of blood pressure in a child with atopic dermatitis treated with cyclosporin. *British Journal of Dermatology* 2002;147(1):183–4.

449. van Meurs T. Extreme rises in serum alkaline phosphatase in children with atopic dermatitis after intervention treatment with cyclosporin A. *Pediatric Dermatology* 1998;15(6):483.

450. Heddle RJ, Soothill JF, Bulpitt CJ, *et al.* Combined oral and nasal beclomethasone diproprionate in children with atopic eczema: a randomised controlled trial. *British Medical Journal* 1984;289(6446):651–4.

451. Galli E, Chini L, Moschese V, *et al.* Methylprednisolone bolus: A novel therapy for severe atopic dermatitis. *Acta Paediatrica* 1994;83(3):315–17.

452. Sonenthal KR, Grammer LC, Patterson R. Do some patients with atopic dermatitis require long-term oral steroid therapy? *Journal of Allergy and Clinical Immunology* 1993;91(5):971–3.

453. Forte WC, Sumita JM, Rodrigues AG, *et al.* Rebound phenomenon to systemic corticosteroid in atopic dermatitis. *Allergologia et Immunopathologia* 2005;33(6):307–11.

454. Murphy LA. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *British Journal of Dermatology* 2002;147(2):308–15.

455. Murphy LA. Azathioprine as a treatment for severe atopic eczema in children with a partial thiopurine methyl transferase (TPMT) deficiency. *Pediatric Dermatology* 2003;20(6):531–4.

456. Goujon C, Berard F, Dahel K, *et al.* Methotrexate for the treatment of adult atopic dermatitis. *European Journal of Dermatology* 2006;16(2):155–8.

457. Weatherhead SC, Wahie S, Reynolds NJ, *et al.* An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. *British Journal of Dermatology* 2007;156(2):346–51.

458. Hanifin JM, Schneider LC, Leung DY, *et al.* Recombinant interferon gamma therapy for atopic dermatitis. *Journal of the American Academy of Dermatology* 1993;28(2 Pt 1):189–97.

459. Stevens SR, Hanifin JM, Hamilton T, *et al.* Long-term effectiveness and safety of recombinant human interferon gamma therapy for atopic dermatitis despite unchanged serum IgE levels. *Archives of Dermatology* 1998;134(7):799–804.

460. Schneider LC. Long-term therapy with recombinant interferon-gamma (rIFN-gamma) for atopic dermatitis. *Annals of Allergy, Asthma, and Immunology* 1998;80(3):263–8.

461. Noh GW. Blood eosinophils and serum IgE as predictors for prognosis of interferon-gamma therapy in atopic dermatitis. *Allergy* 1998;53(12):1202–7.

462. Pung YH, Vetro SW, Bellanti JA. Use of interferons in atopic (IgE-mediated) diseases. *Annals of Allergy* 1993;71(3):234–8.

463. Horneff G. Interferon-gamma for treatment of severe atopic eczema in two children. *Clinical Investigator* 1994;72(5):400–3.

464. Patel L. Interferon gamma in children with severe refractory atopic dermatitis. *Journal of Dermatological Treatment* 1996;7(Suppl 3): S21–23.

465. Jolles S. A review of high-dose intravenous immunoglobulin treatment for atopic dermatitis. *Clinical and Experimental Dermatology* 2002;27(1):3–7.

466. Medicines and Healthcare products Regulatory Agency. *Advice to Consumers – The Traditional Herbal Medicines Registration Scheme* [www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=1142].

467. Johnston GA, Bilbao RM, Graham-Brown RA. The use of complementary medicine in children with atopic dermatitis in secondary care in Leicester. *British Journal of Dermatology* 2003;149(3):566–71.

468. Hughes R, Ward D, Tobin AM, *et al.* The use of alternative medicine in pediatric patients with atopic dermatitis. *Pediatric Dermatology* 2007;24(2):118–20.

469. Witt CM, Ludtke R, Baur R, *et al.* Homeopathic medical practice: long-term results of a cohort study with 3981 patients. *BMC Public Health* 2005;5:115.

470. Mohan GR, Anandhi KS. Efficacy of homeopathic drugs in dermatitis of atopic diathesis: a clinical study. *Homoeopathic Links* 2003;16(4):257–62.

471. Sheehan MP, Atherton DJ. A controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema. *British Journal of Dermatology* 1992;126(2):179–84.

472. Sheehan MP, Atherton DJ. One-year follow up of children treated with Chinese medicinal herbs for atopic eczema. *British Journal of Dermatology* 1994;130(4):488–93.

473. Zhang W, Leonard T, Bath-Hextall F, Chambers CA, Lee C, Humphreys R, Williams HC. Chinese herbal medicine for atopic eczema. *Cochrane Database of Systematic Reviews* 2005;(4).

474. Hon K, Leung TF, Wong Y, *et al.* A pentaherbs capsule as a treatment option for atopic dermatitis in children: an open-labeled case series. *American Journal of Chinese Medicine* 2004;32(6):941–50.

475. Perharic-Walton L, Murray V. Toxicity of Chinese herbal remedies. *Lancet* 1992;340(8820):673–4.

476. Kane JA, Kane SP, Jain S. Hepatitis induced by traditional Chinese herbs; possible toxic components. *Gut* 1995;36(1):146–7.

477. Perharic L, Shaw D, Leon C, *et al.* Possible association of liver damage with the use of Chinese herbal medicine for skin disease. *Veterinary and Human Toxicology* 1995;37(6):562–6.

478. Ferguson JE, Chalmers RJ, Rowlands DJ. Reversible dilated cardiomyopathy following treatment of atopic eczema with Chinese herbal medicine. *British Journal of Dermatology* 1997;136(4):592–3.

479. Lord GM, Tagore R, Cook T, *et al.* Nephropathy caused by Chinese herbs in the UK. *Lancet* 1999;354(9177):481–2.

480. Hughes JR, Higgins EM, Pembroke AC. Oral dexamethasone masquerading as a Chinese herbal remedy. *British Journal of Dermatology* 1994;130(2):261.

481. Keane FM, Munn SE, du Vivier AW, *et al.* Analysis of Chinese herbal creams prescribed for dermatological conditions. *British Medical Journal* 1999;318(7183):563–4.
482. Ramsay HM, Goddard W, Gill S, *et al.* Herbal creams used for atopic eczema in Birmingham, UK illegally contain potent corticosteroids. *Archives of Disease in Childhood* 2003;88(12):1056–7.
483. Medicines and Healthcare products Regulatory Agency. *Safety of Herbal Medicinal Products.* 2002.
484. Sokel B. A comparison of hypnotherapy and biofeedback in the treatment of childhood atopic eczema. *Contemporary Hypnosis* 1993;10(3):145–54.
485. Derrick EK, Karle H, Darley CR. The use of self-hypnosis and guided imagery techniques in the management of childhood eczema. *Journal of Dermatological Treatment* 1994;5(2):83–4.
486. Stewart AC, Thomas SE. Hypnotherapy as a treatment for atopic dermatitis in adults and children. *British Journal of Dermatology* 1995;132(5):778–83.
487. Schachner L, Field T, Hernandez-Reif M, *et al.* Atopic dermatitis symptoms decreased in children following massage therapy. *Pediatric Dermatology* 1998;15(5):390–5.
488. Anderson C. Evaluation of massage with essential oils on childhood atopic eczema. *Phytotherapy Research* 2000;14(6):452–6.
489. Al-Waili NS. Topical application of natural honey, beeswax and olive oil mixture for atopic dermatitis or psoriasis: partially controlled, single-blinded study. *Complementary Therapies in Medicine* 2003;11(4):226–34.
490. Kalus U, Pruss A, Bystron J, *et al.* Effect of *Nigella sativa* (black seed) on subjective feeling in patients with allergic diseases. *Phytotherapy Research* 2003;17(10):1209–14.
491. Bordoni A, Biagi PL, Masi M, *et al.* Evening primrose oil (Efamol) in the treatment of children with atopic eczema. *Drugs Under Experimental and Clinical Research* 1988;14(4):291–7.
492. Biagi PL, Bordoni A, Hrelia S, *et al.* The effect of gamma-linolenic acid on clinical status, red cell fatty acid composition and membrane microviscosity in infants with atopic dermatitis. *Drugs Under Experimental and Clinical Research* 1994;20(2):77–84.
493. Takwale A, Tan E, Agarwal S, *et al.* Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial. *British Medical Journal* 2003;327(7428):1385.
494. Withdrawal of Epogam and Efamast. *Current Problems in Pharmacovigilance* 2002;28:12.
495. Witt C, Keil T, Selim D, *et al.* Outcome and costs of homoeopathic and conventional treatment strategies: A comparative cohort study in patients with chronic disorders. *Complementary Therapies in Medicine* 2005;13(2):79–86.
496. Hampel P, Rudolph H, Petermann F, *et al.* Stress management training for children and adolescents with atopic dermatitis during inpatient rehabilitation. *Dermatology and Psychosomatics* 2001;2(3):116–22.
497. Ersser S, Latter S, Surridge H, Buchanan P, Satherley P, Welbourne S. Psychological and educational interventions for atopic eczema in children. *Cochrane Database of Systematic Reviews* 2006:(1).
498. Staab D, Diepgen TL, Fartasch M, *et al.* Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *British Medical Journal* 2006;332(7547):933–8.
499. Broberg A, Kalimo K, Lindblad B, *et al.* Parental education in the treatment of childhood atopic eczema. *Acta Dermato-Venereologica* 1990;70(6):495–9.
500. Grillo M, Gassner L, Marshman G, *et al.* Pediatric atopic eczema: the impact of an educational intervention. *Pediatric Dermatology* 2006;23(5):428–36.
501. Carr A, Patel R, Jones M, *et al.* A pilot study of a community pharmacist intervention to promote the effective use of emollients in childhood eczema. *The Pharmaceutical Journal* 2007;278:319–22.
502. Fischer G. Compliance problems in paediatric atopic eczema. *Australasian Journal of Dermatology* 1996;37 Suppl 1:S10–13.
503. Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. *British Journal of Dermatology* 2000;142(5):931–6.
504. Cork MJ, Britton J, Butler L, *et al.* Comparison of parent knowledge, therapy utilization and severity of atopic eczema before and after explanation and demonstration of topical therapies by a specialist dermatology nurse. *British Journal of Dermatology* 2003;149(3):582–9.
505. Ohya Y, Williams H, Steptoe A, *et al.* Psychosocial factors and adherence to treatment advice in childhood atopic dermatitis. *Journal of Investigative Dermatology* 2001;117(4):852–7.
506. Baum WF, Schneyer U, Lantzsch AM, *et al.* Delay of growth and development in children with bronchial asthma, atopic dermatitis and allergic rhinitis. *Experimental and Clinical Endocrinology and Diabetes* 2002;110(2):53–9.
507. David TJ. Short stature in children with atopic eczema. *Acta Dermato-Venereologica. Supplementum* 1989;144:41–4.
508. Patel L. Linear growth in prepubertal children with atopic dermatitis. *Archives of Disease in Childhood* 1998;79(2):169–72.
509. Pike MG, Chang CL, Atherton DJ, *et al.* Growth in atopic eczema: a controlled study by questionnaire. *Archives of Disease in Childhood* 1989;64(11):1566–9.
510. Kristmundsdottir F, David TJ. Growth impairment in children with atopic eczema. *Journal of the Royal Society of Medicine* 1987;80(1):9–12.
511. Patel L, Clayton PE, Jenney ME, *et al.* Adult height in patients with childhood onset atopic dermatitis. *Archives of Disease in Childhood* 1997;76(6):505–8.
512. Massarano AA, Hollis S, Devlin J. Growth in atopic eczema. *Archives of Disease in Childhood* 1993;68(5):677–9.
513. Morava E, Molnar D. Somatometric studies in allergic children. *Padiatrie und Padologie* 1994;29(2):35–8.
514. Ellison JA. Pattern of growth and adiposity from infancy to adulthood in atopic dermatitis. *British Journal of Dermatology* 2006;155(3):532–8.
515. Carrington LJ, Langley-Evans SC. Wheezing and eczema in relation to infant anthropometry: evidence of developmental programming of disease in childhood. *Maternal and Child Nutrition* 2006;2(1):51–61.
516. Fergusson DM, Crane J, Beasley R, *et al.* Perinatal factors and atopic disease in childhood. *Clinical and Experimental Allergy* 1997;27(12):1394–401.
517. Eichenfield L. Evaluation of adrenal suppression of a lipid enhanced, topical emollient cream formulation of hydrocortisone butyrate 0.1% in treating children with atopic dermatitis. *Pediatric Dermatology* 2007;24(1):81–4.
518. Turpeinen M. Effect of percutaneous absorption of hydrocortisone on adrenocortical responsiveness in infants with severe skin disease. *British Journal of Dermatology* 1986;115(4):475–84.
519. Heuck C. Knemometry in children with atopic dermatitis treated with topical glucocorticoids. *Pediatric Dermatology* 1998;15(1):7–11.

520. Wolthers OD, Heuck C, Ternowitz T, *et al.* Insulin-like growth factor axis, bone and collagen turnover in children with atopic dermatitis treated with topical glucocorticosteroids. *Dermatology* 1996;192(4):337–42.

521. Aylett SE, Atherton DJ, Preece MA. The treatment of difficult atopic dermatitis in childhood with oral beclomethasone dipropionate. *Acta Dermato-Venereologica. Supplementum* 1992;(176):123–5.

522. Woo WK. Iatrogenic adrenal gland suppression from use of a potent topical steroid. *Clinical and Experimental Dermatology* 2003;28(6):672–3.

523. Bode HH. Dwarfism following long-term topical corticosteroid therapy. *JAMA: the Journal of the American Medical Association* 1980;244(8):813–14.

524. Caffarelli C, Cavagni G, Deriu FM, Zanotti P, Atherton DJ. Gastrointestinal symptoms in atopic eczema. *Archives of Disease in Childhood* 1998;78(3):230–4.

525. Agostoni C. Growth pattern of breastfed and nonbreastfed infants with atopic dermatitis in the first year of life. *Pediatrics* 2000; 106:(5)E73.

526. Isolauri E, Sutas. Elimination diet in cow's milk allergy: risk for impaired growth in young children. *Journal of Pediatrics* 1998;132(6):1004–9.

527. Laitinen K. Evaluation of diet and growth in children with and without atopic eczema: follow-up study from birth to 4 years. *British Journal of Nutrition* 2005;94(4):565–74.

528. Estrada-Reyes E, Garcia-Hernandez. Effect of extensively hydrolyzed milk formula on growth and resistance to bronchitis and atopic dermatitis in infants and toddlers. *Journal of Investigational Allergology and Clinical Immunology* 2006;16(3):183–7.

529. McCormick A, Fleming D, Charlton J. *Morbidity Statistics from General Practice: Fourth National Study 1991–1992*. London: HMSO; 1995.

530. Primary Care Dermatology Society and British Association of Dermatologists. Guidelines for the management of atopic eczema. *eGuidelines* 2006;28:372–5.

531. Wolkerstorfer A, Laan MP, Savelkoul HF, *et al.* Soluble E-selectin, other markers of inflammation and disease severity in children with atopic dermatitis. *British Journal of Dermatology* 1998;138(3):431–5.

532. Koning H, Neijens HJ, Baert MR, *et al.* T cell subsets and cytokines in allergic and non-allergic children. I. Analysis of IL-4, IFN-gamma and IL-13 mRNA expression and protein production. *Cytokine* 1997;9(6):416–26.

533. Frezzolini A, Paradisi M, Ruffelli M, *et al.* Soluble CD30 in pediatric patients with atopic dermatitis. *Allergy* 1997;52(1):106–9.

534. Broberg A, Svensson A, Borres MP, *et al.* Atopic dermatitis in 5–6-year-old Swedish children: cumulative incidence, point prevalence, and severity scoring. *Allergy* 2000;55(11):1025–9.

535. Burr ML, Butland BK, King S, *et al.* Changes in asthma prevalence: two surveys 15 years apart. *Archives of Disease in Childhood* 1989;64(10):1452–6.

536. Wolkerstorfer A, Wahn U, Kjellman NI, *et al.* Natural course of sensitization to cow's milk and hen's egg in childhood atopic dermatitis: ETAC study group. *Clinical and Experimental Allergy* 2002;32(1):70–3.

537. Bohme M, Wickman M, Lennart NS, *et al.* Family history and risk of atopic dermatitis in children up to 4 years. *Clinical and Experimental Allergy* 2003;33(9):1226–31.

538. Halkjaer LB, Loland L, Buchvald FF, *et al.* Development of atopic dermatitis during the first 3 years of life: the Copenhagen prospective study on asthma in childhood cohort study in high-risk children. *Archives of Dermatology* 2006;142(5):561–6.

539. Kuehr J, Frischer T, Karmaus W, *et al.* Clinical atopy and associated factors in primary-school pupils. *Allergy* 1992;47(6):650–5.

540. Lehtonen EP, Holmberg-Marttila D, Kaila M. Cumulative prevalence of atopic eczema and related skin symptoms in a well-baby clinic: a retrospective cohort study. *Pediatric Allergy and Immunology* 2003;14(5):405–8.

541. Vasar M, Julge K, Bjoksto B. Development of atopic sensitization and allergic diseases in early childhood. *Acta Paediatrica* 2000;89(5):523–7.

542. Vierrucci A, Novembre E, de MM, *et al.* Reliability of tests for specific IgE to food in atopic dermatitis. *Allergy, Supplement* 1989;44(9):90–6.

543. Hebert AA, Friedlander SF, Allen DB. Topical fluticasone propionate lotion does not cause HPA axis suppression. *Journal of Pediatrics* 2006;149(3):378–82.

544. Wahn U. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: first results of ETAC. Early Treatment of the Atopic Child. *Pediatric Allergy and Immunology* 1998;9(3):116–24.

545. Curtis L, Netten A. *Unit Costs of Health and Social Care*. Canterbury: Personal and Social Services Research Unit, University of Kent at Canterbury; 2006.

546. Stein K, Dyer M, Crabb T, *et al.* A pilot Internet "value of health" panel: recruitment, participation and compliance. *Health and Quality of Life Outcomes* 2006;4:90.

547. Niggemann B, Reibel S, Roehr C, *et al.* Predictors of positive food challenge outcome in non-IgE mediated reactions to food in children with atopic dermatitis. *Journal of Allergy and Clinical Immunology* 2001;108(6):1053–8.

548. Sampson H. Role of immediate food hypersensitivity in the pathogenesis of atpic dermatitis. *Journal of Allergy and Clinical Immunology* 1983;71(5):473–80.

549. Sampson H, McCaskill C. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *The Journal of Pediatrics* 1985;107(5):669–75.

550. Burks A, James J, Hiegel A, *et al.* Atopic dermatitis and food hypersensitivity reactions. *The Journal of Pediatrics* 1998;132(1):132–6.

Index

Notes
All entries refer to atopic eczema unless otherwise noted.
vs denotes comparisons.

Other NICE guidelines produced by the National Collaborating Centre for Women's and Children's Health include:

- **Antenatal care: routine care for the healthy pregnant woman**
- **Fertility: assessment and treatment for people with fertility problems**
- **Caesarean section**
- **Type 1 diabetes: diagnosis and management of type 1 diabetes in children and young people**
- **Long-acting reversible contraception: the effective and appropriate use of long-acting reversible contraception**
- **Urinary incontinence: the management of urinary incontinence in women**
- **Heavy menstrual bleeding**
- **Feverish illness in children: assessment and initial management in children younger than 5 years**
- **Urinary tract infection in children: diagnosis, treatment and long-term management**
- **Intrapartum care: care of healthy women and their babies during childbirth**

Guidelines in production include:

- **Surgical management of otitis media with effusion**
- **Antenatal care (update)**
- **Diabetes in pregnancy**
- **Induction of labour (update)**
- **Surgical site infection**
- **Diarrhoea and vomiting in children under 5**
- **When to suspect child maltreatment**
- **Meningitis and meningococcal disease in children**
- **Neonatal jaundice**

Enquiries regarding the above guidelines can be addressed to:

National Collaborating Centre for Women's and Children's Health
King's Court, Fourth Floor
2-16 Goodge Street
London
W1T 2QA
enquiries@ncc-wch.org.uk

A version of this guideline for the public is available from the NICE website (www.nice.org.uk/CG057PublicInfoEnglish) or from the NHS Response Line (0870 1555 455); quote reference number N1428.

ISBN 978-1-904752-42-4
9 781904 752424

Published by the Royal College of Obstetricians and Gynaecologists.
To purchase further copies and for a complete list of RCOG Press titles, visit: **www.rcogbookshop.com**

RCOG Press