The Yorkshire Atopic Eczema Management Guidelines

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Although there is no 'cure', the symptoms of atopic eczema can be treated very effectively. In practice, many of the problems in managing eczema centre on the difficulty of using complicated, messy and time-consuming treatments. An increased understanding by families of the use of these treatments, and practical help in their usage are critical to ensuring compliance and improved treatment of the eczema [1]. There are some RCT data to support the use of parental training programmes [2]. The provision of accessible facilities for demonstration of these treatments and the subsequent support of families is seen to be essential.

Table 1 Definition of the levels of evidence used in preparation of the guidelines

Level	Type of evidence
Ia	evidence obtained from meta-analysis of randomised controlled trials (RCT)
Ib	evidence obtained from at least one randomised controlled trial
IIa	evidence obtained from at least one well-designed controlled study without randomisation
IIb	evidence obtained from at least one other type of well-designed quasi-experimental study
III	evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
Grade of Recommendation	
A	there is good evidence to support the use of the procedure
B	there is fair evidence to support the use of the procedure
C	there is poor evidence to support the use of the procedure
D	there is fair evidence to support the rejection of the use of the procedure
E	there is good evidence to support the rejection of the use of the procedure

Emollients

Emollients are the basis of the management of atopic eczema, although good data to support this view are lacking [3] (Grade B, level III).

Ointments are preferable to creams as they have a lower or non-existent water content [4-6] and may not need added preservatives. The patient's choice is, in practice however, very important in order to improve compliance. The consensus is that emollients should be applied as liberally and as frequently as necessary to maintain moist skin but there have been no clinical trials to investigate the optimum dose range. A dose of 250g/week of an emollient cream/ointment for a child and 500g/week for an adult was recommended in a previous British Association of Dermatology (BAD) report [7] although the needs do vary between

individuals and over time. The emollient wet wrapping technique may require at least 500g of emollient cream or ointment per week [8, 9]. Emollients may contain humectants, which are substances that attract water to themselves (such as urea, lactate, and pyrolidone carboxylic acid). There are some data to support their use [10], although they have some irritant effects and they may be most useful, then, in some body sites such as the feet. Some emollients contain other additives that may sting, such as preservatives [10]. This stinging is more of a problem when the skin is particularly dry or inflamed but there are some emollients, which do this more regularly than others. When skin is really dry, rapid but transient development of redness is seen after the application of almost any emollient. It is worth warning families of this or they may feel that the emollient is making the eczema worse.

Soaps and detergents de-grease the skin and therefore should not be used.

Bath oils may be helpful but the dominant need is for the use of emollient ointments.

The use of very greasy emollients may cause folliculitis in hairy skin and may compound infection. It may be necessary then to reduce the emollient usage in hairy areas, and to actively treat infection first and then work on emollient application later.

Emollients may also be less well tolerated in hot weather.

Recommendations

- Emollients are the first line treatment for atopic eczema, having a steroid sparing effect and helping to restore epidermal barrier function (Grade B, level III)
- The quantity of emollients used is often inadequate. In moderate to severe widespread eczema babies usually need at least 250g per week and adults around 500g per week
- Whilst greasy emollients are preferred, patient acceptability is important, so that a range of preparations may have to be tried.

Wet wraps

Wet wraps are a form of occlusive bandaging using tubes of tubular bandage such as Tubifast or Coverflex and stockinette tied together to form a suit [8]. They are constructed in two layers, the bottom layer being damp and the top, dry. More recently the makers of Tubifast have introduced preformed garments for use in eczema, as vests, tights (1 size only 6-24 months), leggings (4 sizes for children over 2 years) and socks. The manufacturers claim that although these are more expensive than the cheapest tubular bandage in the short term they are more cost-effective in the longer term because of better durability with washing even at 60ºC. They may prove to be of considerable value if they increase compliance.

Wet wraps may be used in two ways: either using emollients alone routinely but with steroids in addition, intermittently as required, (in which case copious quantities of the preferred non-irritating emollient are applied). The other way, originally described is to routinely use the wraps with large quantities of a dilute steroid such as 1 in 10 Propaderm or Betnovate 1 in 10. It is the consensus view that wet wraps are best used with emollients alone or with only short

term use of topical steroids in localised areas. That is, they are a means of improving the value of emollients predominantly.

They may be used continuously when the skin is really sore (reapplying emollient at a minimum of every 12 hours) or at night only when things are not so bad. Some patients will require them for long periods, in others they may be used to "nip in the bud" an outbreak of eczema. They are not absolutely contra-indicated in the presence of infection but should be used with great caution.
Wet wraps are not tolerated by many, because of sticking and temperature loss particularly when it is cold. Some will then use just the emollient and a single layer of tubing. Many units recommend emollient wrapping. The first layer of cotton tubing is applied over emollients, then another layer of emollient and finally a second layer of tubing is applied.

Occlusion

Chronic scratching produces lichenification and this may be self-perpetuating. Occlusion with a hydrocolloid dressing over a steroid changed twice a week may help here. Thin comfortable options include Duoderm Thin.

Topical steroids

Topical steroids are the second line of treatment for atopic eczema after emollients. In the UK, four categories of potency are used (British National Formulary). Studies generally show that within a potency group there is little difference in clinical efficacy. Diluting steroid preparations does not necessarily affect the potency or reduce the risk of side effects. There are no RCT data to support the practice [3]. Ointments (oil-based) are more effective than creams, although creams and lotions (water-based, not alcoholic) are useful when the skin is inflamed. Steroid absorption, and hence efficacy, is increased by base ingredients such as propylene glycol, urea and salicylic acid, by body site and by occlusion. Patients need to understand that side effects are related to the potency of the steroid, the amount used and site of application. The use of brand names may improve communication with other members of the health team.

Patients also need to understand how much to apply and for how long. The Fingertip Unit (FTU) is used as a guide for patients, as to how much cream should be applied. It is the volume of steroid expressed from a 5mm diameter nozzle, to cover an adult index finger t from the distal crease to the tip. A guide to the application of cream per body part in children is given below, based on predicted and actual amounts applied by patients [11, 12]. Lewis-Jones simply illustrates the FTU as "one FTU" covers the area of skin covered by two adult hands.

Table 2 : Application of steroid by FTU by body site

Age	Face and neck	Arm and hand	Leg and foot	Anterior trunk	Posterior trunk
3 to 6 months	1	1	1.5	1	1.5
1 to 2 years	1.5	1.5	2	2	3
3 to 5 years	1.5	2	3	3	3.5
6 to 10 years	2	2.5	4.5	3.5	5

It is also crucial to prescribe suitable quantities for the body area requiring treatment. Table 3 below gives the weekly requirement of ointment in grams for twice daily treatment. Although the newer steroids are marketed specifically as ‘once-daily preparations’ there is evidence that for all steroids ‘once daily’ will suffice after one week of twice daily application [13, 14] [15].

It is the consensus view that for every gram of steroid prescribed, a minimum of approximately 10 grams of emollient should be prescribed.

Table 3: Quantities of steroid by body site needed per week in grams

Age	Whole body	Arms and legs	Trunk
6 months	35	20	15
1 year	45	20	15
4 years	60	35	20
8 years	90	50	35
12 years	120	65	45

16 years	155	85	55
Adult	170	90	60

What strength of steroid is appropriate to use in young children?
Some recommend using weak and moderately potent steroids only [16]. Others recommend stronger steroids to troublesome areas on a short-term basis or when the eczema is particularly severe, to prevent chronicity [17]. There are few RCT data to support either pattern of steroid usage. A recent study compared the use of short bursts of Betnovate with prolonged use of a milder steroid in 174 children with mild to moderate eczema and showed no difference in eczema control [18]. There is a consensus towards the use of intermittent short bursts of moderate or very potent steroids for up to two to four weeks, with treatment holidays [7, 19].

Children, particularly below the age of 2 years, have high surface to body ratios and are therefore more prone to systemic side effects such as hypothalamus-pituitary axis (HPA) depression and growth retardation. HPA axis depression in children is demonstrable with very potent steroids such as Dermovate and with potent steroids such as Betnovate although it is reversible to some extent [20-22]. The modern steroids exhibiting rapid liver metabolism such as Elocon and Cutivate, appear to give much less significant depression and are therefore preferable as the choice of potent steroid [23]. Many children with severe eczema also have asthma requiring treatment with inhaled steroids which can certainly cause adrenal suppression [24]. The ill-defined symptoms (anorexia, abdominal pain, weight loss, tiredness, headache, decreased levels of consciousness and fits) should therefore be borne in mind in children using inhaled steroids, especially fluticasone (Flixotide or Seretide).

Local side effects of steroids are mainly cutaneous atrophy [25, 26] and allergic contact dermatitis [27]. The degree of skin thinning appears to correlate to some degree with potency although again Cutivate and Elocon appear to offer a better therapeutic ratio [28], although long term data on side effects are lacking.Peri-oral dermatitis can occur with Elocon in the same way that it does with Betnovate

Topical steroids should be kept out of the eye because of the risk of precipitating glaucoma. Because of rubbing or smearing during sleep, it is best to avoid of the use of potent steroids in this area.

The weakest effective steroid, should be used at any time. However, a short period of use of potent steroids may abort the development of a severe episode of eczema and indeed for children with moderately severe eczema, can be valuable. Eczema often becomes progressively worse in a "vicious cycle" way, with the cycle being that of itch/scratch/itch and judicious use of potent steroids in conjunction with emollients may abort this. The consensus view is therefore that the intermittent application of potent steroids, perhaps for a few days to each body site, every few weeks is effective and indeed essential, in patients with severe eczema. There are some RCT to suggest that fluticasone proprionate used twice weekly after a flare has been cleared with the same steroid, prevents relapse [29]. There is some evidence that topical steroids used for short periods over long periods of time do not produce skin thinning [30]. Steroid tachyphylaxis may occur .

Steroids combined with antifungals and antibacterials (by the manufacturer), may be particularly useful for the flexures and in the presence of recurrent infection, but there are no RCTs to support their use [3].

General principles suggest treatment should continue for a few days longer than it takes for clinical resolution to reduce the chance of rebound.

Recommendations

- The steroid of choice is the weakest onewhich will clear the eczema at any time. Patients may benefit from having more than 1 steroid for use in different sites and for different levels of severity. It may be useful to describe this as the steroid ladder, so that the patient needs to go up and down the steroid strengths (rungs)
- Use of new generation potent steroids intermittently is effective and safe in moderate to severe eczema but families must understand what intermittent means
- The use of the most potent topical steroids such as Dermovate is associated with cutaneous atrophy and hypothalamus/pituitary axis depression, particularly in children, although some of these effects are reversible (Grade A, level IIA). The use of such steroids should therefore be limited
- The fingertip method is useful in describing how much steroid should be applied although demonstration in clinic is also recommended

Topical treatment with tar

Tar applied to eczematous skin has been used much in the past but can be very irritating. There are also some theoretical anxieties about the risk of carcinogenesis in the long term. It is probably best used in the form of bandages to limbs when chronic excoriation or nodular prurigo is a problem. Bandages may be left in place for 3/4 days then changed. Ichthammol is less irritating than coal tar and is therefore preferred, particularly as there appears to be no risk of carcinogenesis. It may be applied as an ointment BP applied 1-3 times a day (10% preparation)- as a zinc and ichthammol cream or as a zinc paste and ichthammol bandage (Icthaband or Icthopaste). 1% ichthammol zinc oxide ointment is soothing in patients reluctant to use steroids

Scalp Treatments

The scalp is difficult to treat in practical terms because of the hair but otherwise the treatment is essentially the same as for eczema elsewhere. That is, that the mainstays of treatment are emollients and topical steroids. Cosmetic needs mean that oils e.g. olive oil may be more applicable as emollients in this site, and that gels or liquids are preferred vehicles for steroids. A particular problem in the scalp however is that scaling may be marked and indeed adherent scale may be considerable. In these circumstances methods must be devised to remove scale. In children with eczema softening of the scale with oil and removal by hand or using a comb may be most effective. In older patients tar shampoos and tar and salicylic acid preparations may be useful to control this problem.

Topical Tacrolimus

Topical Tacrolimus has been shown to be an effective treatment for eczema but it is not yet clear how its cost/efficacy compares with that of topical steroids. In a trial of 316 patients with moderate to severe eczema, 54% cleared in 1 week, 81% in 6 months and 86% in 12 months [31]. Although Tacrolimus may produce a burning sensation of the skin there is no evidence that it causes cutaneous atrophy [3]. It was licenced in April 2002 for use in patients with eczema over the age of 2 years. The long-term risks of treatment are as yet unclear.

Tacrolimus is a macrolide produced by streptomyces tsukabaensis, a fungus growing in the soil of Mount Tsukuba. It is a ciclosporin-like drug which is however much better absorbed when applied to the skin.. There is said to be minimal absorption = <5% oral tacrolimus even with extensive disease and absorption 'stops" as the inflamed skin heals, although anecdotally, significant systemic absorption has been reported in erythroderma [32]. Its mode of action is immuno-modulatory. It inhibits T cell transcription via the calcineurin pathway and reduces IL-3, Il-4, Il-5, GM-CSF, TNF α and IFN-α release. It may also have effects via the steroid receptor and TGF β. It also reduces
release mediators from mast cells and basophils. Any absorbed Tacrolimus is metabolised in the liver by the P450 enzyme CYP3A4. It should not be used under occlusion. *[33]*

Tacrolimus ointment (0.1% and 0.03%) can be used for the treatment of moderate to severe atopic eczema that is unresponsive to conventional therapy. In clinical trials in adults, 0.1% was more effective than 0.03% but not in children, therefore 0.03% only is recommended for children over the age of 2 years and under 16 years. There have been relatively few clinical trials published in which topical Tacrolimus has been compared with potent steroids but two published in Japanese were reviewed in translation and it was suggested that it is as effective in clearing eczema as betamethasone valerate or aclometasone dipropionate [34]. A recent review suggested that more than 16,000 persons suffering from atopic dermatitis have now been enrolled in clinical studies of Tacrolimus. One third of patients with moderate to severe atopic dermatitis experienced over 90% improvement in their disease over a 12-week treatment period and up to 70% of patients had over 50% improvement. A 1-year treatment led to more than 90% improvement in 75% of patients [35]. The cost-effectiveness of Tacrolimus as compared with potent steroids needs to be assessed. Preliminary modelling using published outcomes data suggests that it might be at least as cost effective [36].

The BNF states that it should only be prescribed by dermatologists and physicians with extensive experience in the treatment of atopic eczema with immunomodulatory therapy. It is the Consensus that Tacrolimus treatment should be initiated only by hospital dermatologists I but maintenance therapy may be supervised in primary care according to protocol.

Side effects of usage are:-

- Infection particularly herpes maybe increased in one study 4/316 patients developed severe infection requiring admission [31]
- Burning sensation of the skin, usually temporary, is common [31]
- Occasionally inflammatory flare

Benefits of Tacrolimus therapy

- No atrophy
- Can be used on the face
- In clinical trials longer time to relapse

Although Tacrolimus clearly has a valuable role in the treatment of eczema, its use is still being evaluated. It may be used when eczema has resolved in conventional means, to prevent relapse or may be used to clear active eczema. It is not yet clear in which way it is most useful. It is a potent immuno-modulatory drug, which is not usually absorbed in significant quantities but could conceivably have co-carcinogenic effects within the skin and its use should therefore be restricted to facial eczema or troublesome unresponsive eczema in other sites, particularly those vulnerable to steroid side effects.. Care should also be taken to avoid sun exposure when the drug is being used. It should not be used with phototherapy.

Pending results of long term trials therefore, it seems prudent to suggest that Tacrolimus be used intermittently: to induce a period of stability, rather than in the long term.

Pimecrolimus (Elidel)

This drug is an ascomycin derivative, which is also a non-steroidal inhibitor of inflammatory cytokines. It has a similar action in the skin to Tacrolimus but is weaker as an immuno-modulator being virtually inactive in transplant models. Animal studies have not produced any evidence for cutaneous carcinogenicity. It is available in one strength, 1%, and can be prescribed for patients of 2 years and upwards.

It appears to have a better safety profile than Tacrolimus although it is less effective. It produces a similar burning sensation, but less severely than does Tacrolimus.

A 1 year RCT study in moderate eczema was reported in 713 patients aged 2 to 17 years in which Elidel was compared with vehicle at the first sign of flare. 61% treated with Elidel were without a flare at 6 months compared with 34% treated with vehicle alone. 35% had had to use steroids at 6 months compared with 63% of controls [37].

Pimecrolimus may be a useful adjunct to the treatment of eczema but its role is not yet clear. It is used in a similar way to Tacrolimus and may be safer.

NICE will report on their view of the use of Tacrolimus and Pimecrolimus in 2004.

Antihistamines

The value of anti-histamines overall in eczema is limited[38]. Non-sedative antihistamines have a limited role in the treatment of eczema for the management of associated problems such as urticaria [39]. The published data on their role in eczema are conflicting [40]. There are some data from he Early Treatment of the Atopic Child study (ETAC) to suggest that regular cetirizine has a role in the prevention of atopic disease [41].

Non-sedative antihistamines should be used to give 24 hour cover if urticaria is associated. It is doubtful whether antihistamines have any specific effect on the itch of eczema in the absence of urticarial itch. Sedative antihistamines may be used at night for their sedative effect if the discomfort of eczema seriously disrupts sleep.

A recently launched topical anti-pruritic agent, 5% Doxepin cream remains to be evaluated. This tri-cyclic anti-depressant has anti-histamine properties. It has been reported to induce drowsiness [42] and there are concerns about toxicity due to absorption.

Sodium cromoglycate

There is little evidence for the value of oral sodium cromoglycate in eczema [40].

Contact eczema

Irritants

Atopic individuals are more sensitive to irritants than those with normal skin. Patients more commonly believe that they are allergic to medicaments than can be proven, because so many preparations cause irritation of the skin especially when that skin is inflamed. Irritants applied to the skin, which cause problems include soap and detergents, or wool so avoiding these where possible is recommended.

Contact allergy

A proportion of atopics will develop contact hypersensitivity. In adults, the lowest rate reported was 13% and the highest was 68%. In an experimental situation it seems that atopics have a reduced risk of sensitisation, but in practice because of their regular usage of topicals they have a significant incidence of allergic contact dermatitis particularly to perfumes and steroids. It is prudent to avoid testing during moderate to severe disease activity to minimise the chance of false positive/negative tests. Patch test reactions in atopics must be interpreted with care because they may produce non-specific irritant reactions.

Prevention and avoidance

It would also be wise to prescribe fragrance free products routinely and to avoid sensitizers and irritants.

There are some data to suggest that exposure to arachis oil may induce sensitisation to peanuts [43]. Although refined peanut oil contains very small amounts of peanut protein, the CSM has advised avoidance of arachis oil in patients allergic to peanuts or soya [44] and it is the consensus that this oil should therefore be avoided in skin units.

Career advice to young atopics is important. They should be advised of the risk of hand eczema in wet work in general, and to avoid catering, nursing and hair dressing in particular. Immediate hypersensitivity to latex is an increasing problem since the usage of protective gloves has increased. There is some justification for the use of non-latex based gloves where appropriate.

Recommendations

- Atopics are more susceptible to irritants such as wool and detergents and therefore exposure to these: should be avoided (Grade B level III)
- Allergic contact hypersensitivity may complicate atopic eczema and may be suspected in unresponsive eczema or eczema in unusual patterns when the patient should be referred for patch testing. There is an argument for patch testing all adults with persisting atopic eczema.
- The use of topical preparations with additives, which are more likely to sensitise such as neomycin, should be avoided if possible to reduce the risk of this. Ointments rather than creams are therefore recommended, and the use of topical antibiotics minimised.
- Latex allergy appears to be in increasing problem in atopic individuals and the use of non-latex gloves and complete cessation of use of powdered gloves is essential (Grade B/ level IIA) in atopics and in health care workers manageing atopics.

Bacterial infection

Flares of eczema may result from bacterial infection indicated by the presence of; crusting, weeping, pustulation and/or cellulitis.

The distinction between colonisation and infection (bacteria causing harm) on clinical grounds may be difficult, although the presence of increased numbers of S Aureus correlates with disease severity, and there is therefore an argument for using anti-infective measures when S Aureus is grown from patients with active eczema [45]. In atopic eczema patients nearly 100% of exudative lesions are colonised and this is associated with high nasal carriage rates [46, 47]. The non-involved skin has S. Aureus colonisation rates of around 75%. From up to 25% of lesions, streptococci may be cultured as well as S.Aureus. Streptococcal infection tends to produce more soreness and systemic symptoms.

S Aureus is thought to act as a potent superantigen, exacerbating eczema and is therefore an important therapeutic target [48].

Testing
Bacteriology swabs are useful in order to identify antibiotic resistant strains of S Aureus and detect additional streptococcal infection. Bacterial colonisation may occur however and therefore a decision to treat should be made on clinical grounds. If herpes simplex infection is suspected swabs may be sent for virological culture and a smear/vesicular fluid sent for electron microscopy but treatment should not be deferred till the result is available.

Prevention of infection
Regular bathing (at least daily) is important using bath oil and liberal emollients but avoiding soap. Patients should not share flannels, sponges or towels with other members of the household. Such household articles should be washed on the hot wash cycle of the washing machine. Patients and parents should be taught the early features of infection to allow early treatment. Tubs of ointments should not be left open. Simple clean procedures should be used by patients or parents applying the creams, such as removing cream with clean spoons from the jar, to prevent contamination. Pump dispensers may also be useful.

Wherever possible anti-microbiols such as cetrimide should be used to treat infection or to prevent it, rather than anti-biotics. Lipids and emollients however do neutralise the effect of anti-septics and therefore should be avoided together. If anti-septics are used in the bath emollients therefore should be applied after the patient gets out of the bath. Crystacide is a topical preparation whose anti-septic properties are due to hydrogen peroxide and this may be helpful to use instead of fucidin. However, the data are lacking on how anti-septics should be used to maximise their efficacy and avoid irritation of the skin.

Use of oral antibiotics
Flucloxacilllin is usually the most appropriate antibiotic for treating moderate to severe S.aureus infection although the penetration of skin by the antibiotic is probably better with erythromycin. Erythromycin or a first generation cephalosporin (such as cephadroxil, cephradine or cephaexin) can be used if there is penicillin allergy. Some patients who are penicillin allergic are also allergic to cephalosporins and these should be avoided in those who have type 1 reactions to penicillin. Amoxycillin is usually given if beta-haemolytic streptococci are isolated, although flucloxacillin does have activity against Strep. In patients

who relapse rapidly, staphylococcal carriage in patient and relatives/household members should be investigated. Resistance is a legitimate concern since up to 88% of S.aureus isolates from first time hospital attendees with eczema showed resistance to penicillin and there are concerns about increasing MRSA and Fucidin [49] resistant strains.

Other measures to combat infection
Restoration of the epidermal barrier is important, using emollients [50]. The use of emollients with antiseptic is an attractive proposition but although there is some evidence of reduction of numbers of S Aureus, conclusive evidence of a clinical therapeutic effect is lacking [51]. Potassium permanganate - is an effective, but messy, bath additive and will dry up exudative eczema quickly. It is best prescribed in tablet form and patients need clear written guidance as to how it should be used. It will stain ceramic baths permanently but plastic ones will respond to prompt cleaning with a cream cleaner. There are few published data on the efficacy of potassium permanganate[52].

Potent topical antibiotics are useful for localized infections. In clinical practice however, in recent times increased numbers of organisms resistant to fusidic acid and mupiricin have been recorded and usage should therefore be limited to the short term. In one Yorkshire series, 50% of all skin patients and 78% of inpatients with eczema carried fusidic acid resistant strains [49].

Steroid-antibiotic combinations are effective in clinical practice although evidence for superiority relative to steroids alone is lacking.

35% of normal individuals carry S Aureus in the anterior nares. Other sites of carriage are the axillae (10%), perineum (20%) and toe webs (5%). In patients with severe eczema, carrier rates at all sites approach 100%. S Aureus can be eliminated from the nose by 10 days treatment with an intranasal antibiotic. Re-infection from relatives is common, however, and re-colonization of the nose often occurs in 6-8 weeks.

There is some evidence that both UVB and PUVA have a direct antimicrobial effect both *in vitro* and *in vivo* and treatment of this type may be useful in patients with chronic or recurrent infection.

Treatment of MRSA carriage
- Staff: MRSA may survive for long periods in hospital and home environments and may colonize the skin, throat and nose of staff although staff are rarely the source of an outbreak.
- The prevention of infection and control of spread is achieved by good basic control measures (hand washing, aseptic techniques, ward cleaning, handling of waste, use of disposable gloves and aprons), antibiotic policies and surveillance.
- The Drug and Therapeutics Bulletin has listed recommended treatments for MRSA carriers.
    - It is suggested that nasal carriage may be treated with Bactroban nasal tds for 5 days. The swab should be repeated 2 days later and if still positive Naseptin used or 1% chlorhexidine cream.
    - In the revised guidelines [53] two courses of Bactroban are suggested prior to Naseptin.

- Skin carriage should be treated with bathing for at least 5 days in 4% chlorhexidine or 2% triclosan, twice weekly hair washing in an antiseptic shampoo and the use of hexachlorophane 0.33% powder for carriage in the groin or axillae.

The child who gets infection time after time

Sometimes children may develop repeated severe episodes of impetiginised eczema requiring multiple courses of antibiotics. It is preferable to treat these patients intensively to prevent relapse with antiseptics in the bath and with topicals. Rarely these children may be given long-term antibiotics (for 2-3 months) with good, permanent effect, but such treatment should be avoided wherever possible because of the population risks of antibiotic resistance.

Recommendations

- Bacterial secondary infection is common in eczema and presents as weeping, crusting and pustulation. Widespread infection is with S Aureus plus or minus Streptococci and usually requires treatment with flucloxacillin +/- amoxycillin or erythromycin or a cephalosporin (Grade A)
- More limited infection may respond to topical antibiotics such as fucidin (used for 5 to 7 days) with moderate potency steroids (Grade B)
- The prevention of infection should be discussed with patients. Bathing, use of emollients and the prevention of contamination of topical preparations is recommended (Grade B, level III).
- The role of antiseptics in the bath and the treatment of nasal carriage is unclear but may be useful (Grade C).

Eczema herpeticum

An eruption of herpes simplex more widespread than the typical localised infection, occurring in a patient with atopic eczema, (or a past history of atopic eczema), is termed eczema herpeticum. It is an important and potentially serious infection indicated by the presence of grouped, punched out erosions, or less often vesiculation (eczema herpeticum). It requires a same day dermatology appointment. The severity of eczema herpeticum varies from an infection slightly more widespread than usual, through increasingly extensive cutaneous infection, to cases with viraemia and systemic infection which may be fatal [54-56].

It may develop from primary infection, from endogenous recurrent infection, or from exogenous re-infection. Some studies suggest that eczema herpeticum is more common in severe eczema [57] with primary infection, with systemic steroid use. [57] [54-56]. Recurrent infection occurs in a proportion (50% in one series) [54].

Recommendations

- Ordinary cases of localised recurrent herpes in atopics may be treated with topical acyclovir (Grade C, level IV).

- Milder forms of eczema herpeticum should respond to oral acyclovir

- More severe cases, especially those with systemic toxicity, should be treated early and intravenously [56] (Grade B, level III).

- Preventative advice: atopic eczema patients or parents should be advised that kissing and close contact with a person with an active cold sore should be avoided (Grade A, level IV).

Chicken pox in children
Rarely, severe widespread infection with varicella may occur in patients with atopic eczema [58] although the data do not support a suggestion of a relationship between atopy and severe chicken pox. The use of systemic acyclovir or equivalent in such cases seems appropriate, but is not documented in the literature.

Molluscum contagiosum

Molluscum contagiosum is increased in both incidence and severity in atopic eczema. No form of treatment is painless, and lesions in children should normally be left untreated, or non-inflamed mollusca simply squeezed in rotation. When more definitive treatment is requested and is regarded as appropriate, cryotherapy is the most effective, possibly using topical anaesthetic gel.

Recommendations for immunisation in children with atopic eczema

- Atopic eczema *per se* is not a contraindication to vaccination

- Smallpox vaccination should not be attempted in individuals who have had atopic eczema because of the risk of eczema vaccinatum [59]. Vaccination should also be avoided in individuals whose family members or children have eczema [59]. A concern however is, how reliable self-reported histories would be in an emergency [60].

- An associated allergy to egg would contraindicate yellow fever vaccines because they can contain egg proteins (Grade A, level II-iii). An allergy to egg is a relative contra-indication to the influenza vaccine. That is, this should not be used in patients with a history of anaphylaxis and in others may be used if there are strong indications for its use if appropriate precautions are taken.

- Anaphylaxis is an extremely rare complication of any vaccination. There have been anxieties that egg allergic children may be more likely to develop anaphylactic responses to MMR but there is no evidence that this is so [61]. MMR is not advised in children with known severe systemic reactions to neomycin or gelatin [61] (Grade B, level II).

Postponement of immunisation should occur:

- during febrile illnesses, including bacterial infection of eczema with systemic toxicity, or during severe exacerbations of the eczema for other reasons
- during significant immunosuppression, and for three months afterwards, for example prednisolone 2 mg/ Kg/ day for one week; or 1 mg/ Kg/ day for one month; or lower doses of steroid with other immunosuppressive agents (Level 3)

- Tacrolimus and Pimecrolimus should not be used 4 weeks prior to live vaccination and 2 weeks prior to killed vaccination and for 4 weeks following vaccination.

The role of environmental allergens such as house dust mite

Latex allergy is an increasing problem in atopic patients, as a cause of immediate reactions. The history is usually clear, with immediate responses to exposure in the form of latex gloves and balloons being most common. The suspicion of latex allergy requires referral to a specialist allergy service for investigation by specific IgE test and prick test. Very severely affected patients may experience cross-reaction to certain ingested fruits such as bananas, avocado, figs, chestnuts, orange and kiwi fruit.

The consensus view is that allergic responses are common in atopic eczema to other environmental agents such as pollen, animal dander and the house dust mite, and that this may aggravate or exacerbate eczema. Other expressions of allergy such as urticaria may also occur.

The difficulties in terms of management however are that:-

- Many families find it difficult to take the necessary measures to avoid the allergens either because pets are central to their lives or because dust reduction seems too disruptive
- The value of IgE-based allergy tests is very limited in predicting the value of avoidance measures. Strongly positive specific IgE (>100 kUa/L) may have some clinical relevance but weaker positives need to be interpreted in the clinical context and in light of the total IgE level.
- Even when major efforts are made to avoid exposure to allergens, there may be little apparent effect on the severity of the eczema.

Advice for families where a child has mild to moderate eczema

- It is sensible for families with an atopic history to avoid the purchase of a mammalian pet.
- Such pets, if already an important part of the family must be excluded from bedrooms.
- The family may ask if they should no longer have the pet at home. In these circumstances
    - It may be worth doing a specific IgE test on the basis that a negative test would mean that exclusion of the pet would be unlikely to have an effect
    - If the animal is removed from the house it may take many months for allergen levels to fall, and therefore the resultant clinical benefit would take time to appear.
- It is sensible to reduce dust levels in the child's bedroom by simple measures such as
    - wet dusting
    - regular vacuuming of the carpet.
    - using synthetic or semi-synthetic bedlinen, quilts and pillows and washing all at 60 degrees C at least weekly.
- There are no data to support more aggressive measures.

Advice for families where the eczema is unresponsive to the usual treatment measures

- It seems sensible that in severe eczema where there is evidence of allergy to the house dust mite, that attempts are made to further reduce the level of house dust mite in the home. That is, that it would here be sensible to carry out a specific IgE test. It would be unreasonable to sanction expensive changes in the home without a high IgE level to house dust mite.

- The evidence for the efficacy of avoidance measures is however unfortunately limited. Strict methods are required to reduce house dust mite levels in the home, sufficient to have a measurable effect and the level of clinical improvement as a result is unclear [62]. The Health Technology Assessment document found no RCT in this area.
- The following measures are suggested if the family is keen to try, starting with the patient's bedroom:

Advice on reducing house dust mite levels in the home

- Vacuum daily, when the child is out of the room. There is little evidence to show that high filtration vacuum cleaners are any more effective than ordinary vacuum cleaners, provided that the machines are efficient [63].
- Use synthetic filled bedding that can be washed frequently at 60 degrees C.
- New mattresses are recommended. Bedding and mattresses may be covered with microporous covers although data supporting their use are few
- Air the room well
- Dust surfaces with a damp cloth frequently: at least weekly
- It may be better for small children to play on a cotton or plastic play mat which can be washed rather than on carpet
- Use curtains that can be regularly washed or roller blinds
- Remove soft furnishings and carpets where possible, particularly in the bedroom.
- Wash soft toys weekly at 60 degrees: leaving them in the freezer will reduce levels significantly
- There may be a role for the use of acaricide sprays to reduce the level of house dust mite; however this is controversial and as yet unproven [64]

Food and atopy

Diet is important in eczema

1. Because type 1, or immediate food allergy is common in children with eczema
2. Because in some children under the age of 1 year, eczema appears to be exacerbated by diet
3. Because families often suspect diet is important and may inappropriately restrict a child's diet

Immediate reactions to foods

Food allergy is common in children with atopic eczema, usually to only one food from a list of the eight commonest 'culprits' at some time in their life. Common culprits are milk, egg, peanuts, soya, fish, seafood, tree nuts, lentils and much less commonly, wheat. Food reactions may also occur as cross reactions to foods similar to the primary allergen. So, patients who are allergic to peanuts primarily may also react to tree nuts. Food allergy is much more common in children with eczema, than in those with asthma. These are immediate responses (usually within 2 hours but up to 8 hour after ingestion) and are classified clinically as mild or severe. The duration of food allergy is variable. Following a period of time, clinical tolerance usually develops to milk and egg. Persistence is more likely in fish and tree nut allergy and peanut allergy must currently be regarded as lifelong, although there is increasing evidence that it may resolve in a proportion of persons.

Atopic eczema patients may also have irritant or pharmacologically mediated adverse responses to foods such as tomatoes, which causes confusion and sometimes contributes to inappropriate dietary restriction. This local response is essentially similar to the "oral allergy syndrome" and in both conditions there would not be systemic symptoms or positive specific IgE levels
One of the problems in management generally is the lack of a "perfect" test for food allergy.

<u>Testing for immediate hypersensitivity to foods</u>

The most commonly used tests for environmental allergies are skin prick tests and serum specific IgE concentration measurement, although the gold standard is the double blind placebo controlled oral food challenge test. The principal problem with IgE tests is that false positive results to a variety of substances are extremely common [65]. The use and interpretation of these tests therefore requires special expertise. They have a role in the management of the atopic but it is the consensus view that use of these tests with respect to food allergy should be primarily by experts. These experts might be paediatricians, dermatologists or immunologists provided that they are working in a multidisciplinary setting, with prick test facilities.

There is no justification for specific IgE testing in the absence of a suggestive history of food allergy.

<u>Immediate food responses</u>

Mild immediate responses include contact urticaria to food, generalised urticaria or angio-oedema, diarrhoea or vomiting. Severe responses include laryngeal oedema producing coughing, difficulty in breathing and voice change (in the very young it may present as a baby who cannot cry), bronchospasm and wheeze, collapse, cyanosis, hypotension or acute vasodilatation. Anaphylaxis has been defined in a variety of ways and is used in these guidelines to mean a severe hypersensitivity response. Fortunately anaphylaxis is rare. Deaths due to anaphylaxis almost always occur as a result of bronchospasm and bronchial inflammation. In a UK series all 8 children who died in the period 1990 to 2000 had a history of asthma [66]. The speed of onset of severe

reactions varies greatly. Sudden cardiovascular collapse is very rare. Allergic reactions may progress to more dangerous levels over 30 minutes to a few hours.

Risk factors for fatal anaphylaxis are;
- a history of a severe allergic response in the past
- a history of asthma/bronchospasm either at the time of the hypersensitivity response or prior to it
- previous history of poorly controlled asthma
- vigorous exercise immediately preceding the reaction
- age under 1 year

Recommendations
- There are no laboratory or clinical tests, which will predict the likelihood of a severe reaction in an individual.
- Routine skin prick or tests of specific IgE concentrations to foods in the absence of a suggestive history are not recommended. Both types of test have significant numbers of false positives and their interpretation can be difficult for non specialists (Grade B, level II)
- Patients with mild symptoms should be managed according to protocol below without investigation (level III)
- Patients with severe symptoms should be referred to a specialist for investigation (Grade B)
- Patients with severe reactions to food should be referred to experts for investigation (level III)

Anaphylaxis Kits

Anaphylaxis kits for at risk children should contain anti-histamines and injectable adrenaline, which is used to treat severe allergic responses: it reduces vaso-dilation and therefore oedema, reduces bronchospasm and reduces further histamine and leukotriene release. It should be given into the muscle of the thigh, as absorption is fast and reliable from this site [67]. The dosage recommended by the Drug and Therapuetics Bulletin for use in the community is age and weight dependent:-

• under 6 months	50 micrograms	*Epi-Pen not appropriate*
• 6 months to 6 years	120 micrograms	Epi-Pen or Anapen junior
• 6 to 12 years	250 micrograms	Epi-Pen or Anapen
• adolescent and adult	500 micrograms	Epi-Pen or Anapen

The automatic pre-filled disposable injection devices (Epi-Pen and Anapen) are however only available with 300 micrograms and in junior forms which supply 150 micrograms. Therefore there are no readily prescribable preparations for babies and even the older children are given an approximated dose as above. There is no suitable automatic dosage kit for babies smaller than 15Kg in weight. Families need to be trained to use these devices and EpiPen and Anapen both make training devices. There should also be training provided for schools. EpiPen and Anapen rely upon different techniques and it is preferable therefore to use one or other in one geographical area.

Because there is no test which will predict risk of severe anaphylaxis it may be difficult to decide which children should be prescribed adrenaline and this should therefore be determined at specialist clinics. The indications as suggested by the Drug and Therapeutics Bulletin [67] are listed below.

Indications for the prescription of anaphylaxis kits

- Severe previous responses
- An allergic reaction associated with respiratory symptoms
- An allergic response to only a trace of allergen
- An allergic reaction in a patient who requires inhaled steroids for their asthma

A paediatric anaphylaxis kit should contain

	Weight 10 – 30 kg	Weight > 30kg
Two Adrenaline i.m. injections Chlorpheniramine syrup (2mg/5mls)	Epipen Jr 0.15mg 2 - 4 mg (5 -10 ml)	Epipen Jr 0.3 mg 4 mg (10 mls)

Management of children with mild responses

The majority of children with mild food responses (other than to peanuts) grow out of these reactions early in life. These children can be managed according to the protocol within these guidelines, without recourse to investigation.

1. Take a good history looking for consistency of response. In most instances, the responsible food will be apparent and it will be most commonly milk, egg or nuts with the other 6 foods listed below as less common alternatives. Children not uncommonly are sensitive to eggs cooked by scrambling etc whereas they may tolerate baked eggs in cakes etc.
2. If the history is confusing but suggestive of food allergy, seek the advice of a paediatric dietitian.
3. If the child appears to be allergic to peanut, or egg over the age of 1 year then refer to the specialist food allergy service. It is useful to note that the peanut is a member of the legume family and that there may be cross-reaction with other members of the same family such as peas or beans. A proportion, furthermore, of patients who are allergic to peanuts are allergic to members of the tree nut family such as walnuts or almonds. The investigation of peanut allergy and its management requires specialist expertise.
4. In the presence of a convincing history of allergy to other food such as milk, leading to mild symptoms only, refer to the dietetics service. The exclusion of cow's milk protein, for example, removes a major constituent of the pre-school child's diet.

   The dietitian will
   - Take a dietary history to confirm or refute the diagnosis
   - Monitor growth
   - Provide detailed information on food products and supplements
   - At intervals which vary from 6 to 12 months, after the age of 1 year, carry out dietary challenge. Challenges should be conducted in hospital, under medical supervision with provision for resuscitation.
   - There is some evidence that carrying out RAST tests before challenge is helpful: that is that if a specific IgE level to a food remains very high then testing should be postponed. Sampson has produced the following table which illustrates that the predictive value of tests to foods differ e.g. wheat positives are frequently false and therefore the level given the best performance is 100kUa/L [68]. That is, that some allergens give results which are likely to be significant at low levels such as egg whilst others are only likely to be significant at higher titres, such as wheat.

Allergen	Decision Point kUa/L	Sensitivity	Specificity
Egg	6	64	90
Milk	32	34	100
Peanut	15	57	100
Fish	20	25	100
Soybean	65	24	99
Wheat	100	13	100

Specific IgE tests may be useful when the history is not suggestive of food allergy but the child has been placed on a restricted diet, as false negatives are rare (less than 5%) [69].

Management of high risk individuals who should be referred to an allergy service

The following are indicators for a prompt referral to a specialist unit

- a serious food reaction as above
- mild or severe food reaction in a child with asthma
- a history suggestive of food hypersensitivity which is likely to be lifelong (e.g. peanuts or shellfish allergy)
- when the history is suggestive of egg allergy in a child over 12 months
- failure to thrive (paediatric service)

Eight foods most commonly associated with allergy

Milk	Wheat (not common in relation to eczema)
Eggs	Peanuts*
Shellfish	Soya*
Fish	Tree nuts such as walnuts, brazil nut

* all legumes

Exacerbation of eczema by foods

Smaller proportions of atopic eczema sufferers appear to have food exacerbated eczema, without the immediate reactions to food described above. Most children grow out of this by the age of 3, almost all by the age of 5 years. Exclusion diet studies give good evidence for a role for diet in atopic eczema but the proportion of children who would benefit is unclear. There are no population-based studies on which to base an estimate. Sampson in a tertiary specialist referral setting, in a highly selected population, has estimated that up to 50% of patients in his clinic benefit, but it has been postulated that about 10% of UK hospital atopic eczema cases may be linked to food allergy [70, 71].

The history of the eczema may give a clue to a significant role for a food in its exacerbation. Eczema may have begun when breast milk is replaced by cow's milk, for example, only to improve again, when the baby was changed to soya or casein-hydrolysate milk substitute. Families may give a good history of an exacerbation of eczema every time the child has egg or fish, or merely that the child is unwell after certain foods are taken. Generally speaking, the culprit foods are one or more of the same 'eight foods', as detailed above.

Treatment and management protocols have been developed, based on the child's age, as the younger the child the more likely is a diet to be of value. It is also simply more feasible to introduce a diet under the age of 1 year. A dietitian's help should always be sought if a diet is to be tried.

The following are circumstances in which consideration of a diet should be made:-

1. Severe eczema is defined as eczema unresponsive to the adequate use of emollients and moderate potency steroids.
2. Sudden onset of severe eczema at weaning.
3. A history suggestive of eczema in response to the ingestion of foods.

Although there are randomised double blind trials, which support a beneficial effect of the exclusion of egg or egg and cows' milk in atopics [72], other such trials have shown no beneficial effect [73]. There are a number of methodological problems with these trials and poor compliance. Overall there is evidence that egg and milk free diets may be helpful in a subsection of young children but chances of clinical benefit are poor (improvement in at best 10% of severely affected eczematous children) [70, 71].

As a result of the lack of efficacy of milk and egg free diets related to concerns that the child may be reacting to other foods," few foods" diets have been tried. The only RCT failed to show benefit in 85 children with refractory eczema[74]. Families may non-the-less wish to try such a diet in early weaning. If the diet isn't associated with any improvement in the eczema after 4 to 6 weeks, then parents can be told that food exclusion is not of benefit. Suitable foods would be lamb, rice, potato, pear, brassicae vegetables and sunflower oil in addition to the hydrolysate or amino acid formula milk. An open trial of an elemental diet suggested an improvement where conventional therapies have failed but as it was not a RCT it is difficult to evaluate [75].

Management principles in a child over one year of age

The influence of diet becomes less important and a diet less likely to help as the age of the child increases. It is the Consensus view that some children appear to experience exacerbations of their eczema in response to some common foods and in these children dietary restrictions may be of value. Overall however, dietary restriction in the absence of immediate food responses is most unlikely to be of value.

Diet in neonates

In a systematic review of the published data, Charman found methodological difficulties in much of the data on neonatal feeding. Although the consensus view remains that breast-feeding should be supported there are some anecdotal reports to support the view that in some babies eczema actually may improve when breast-feeding is stopped

There is some anxiety that the early introduction of mixed foods in children with a family history of atopic eczema increases the risk to that child. The consensus is therefore that supplementary foods should not be introduced before the 5th month of life [76]. In atopic families it is therefore sensible to advise exclusive breast feeding and the delayed introduction of eggs and probably fish till the age of one as a preventive measure. The Chief Medical Officer has suggested that breast feeding for 4 to 6 months should be supported as was suggested by a European Consortium [76]. There are some data to support the use of hydrolysed formulae prophylactically in babies with a family history of atopy where breast feeding is abandoned [77].

In babies who develop troublesome eczema, after weaning, which doesn't settle with usual methods, a diet may be tried. The choice is soya (more palatable but 8% of cows milk sensitive babies are however also soya allergic), casein hydrolysed formula such as Nutramigen or fully hydrolysed formula such as Neocate. Neocate is made of free amino acids, is often said to be more palatable than Nutramigen and there is some evidence for benefit compared with hydrolysed formulae in terms of growth [78]. It is unclear whether bottle-fed babies in whom milk allergy is suspected, should be put on Soya milk first or should be given Neocate straight away. Soya has the advantage of palatability and Soya yoghurts are useful but Neocate is likely to be suitable for a greater proportion of babies and is recommended by a European Consortium [76].

Diet in pregnancy and during lactation

Although one study suggested that a small number of babies seem to be affected by foods in their mother's diet [79] there is no good overall evidence that restrictive diets are of benefit in pregnancy. Moreover maternal diets may impair nutrition for the mother and her baby. Peanuts however should be avoided during pregnancy and breast feeding. There is some evidence that egg, nut, soya, fish and milk avoidance during lactation may reduce the risk for a second atopic baby [80], but that this avoidance would not be beneficial for a baby who already has atopic eczema. These results are questioned in the review by Charman et al based on methodological concerns.

It would seem sensible that if there is clear evidence of food allergy in the baby however, that the mother should practice avoidance of the same food.

Food and growth

There is a clear association between poor growth and atopic disease, so that there are good reasons to monitor height and weight. Malnutrition may occur as a result of exclusion diets, so that the dietitian is an essential part of the therapeutic team. Failure to thrive is defined as a failure of the baby to put on adequate weight. Children with severe eczema alone may show a failure to thrive, which is poorly understood but which may be multifactorial. In determining the actual cause of restrictive growth the presence of an immunological disorder such as Wiskott Aldrich syndrome, combined immune deficiency syndrome or hyper IgE syndrome should be looked for..

Recommendations

- A milk, egg and fish free diet should be considered in children under the age of 12 months who have troublesome unresponsive eczema. Such diets require assistance from a paediatric dietitian (Grade A, level I)
- Diets used to treat eczema should be attempted according to the above protocol which is based upon a trial of diet rather than testing (Grade A, level II)
- Diets are less likely to be successful in the treatment of eczema over the age of 12 months
- There is little evidence that maternal diet in pregnancy has an effect on the subsequent risk of eczema and food allergy but it is sensible to avoid peanuts (Grade B, level III)
- There is some evidence that maternal avoidance of antigenic foods during lactation may reduce the risk of atopic disease (Grade B, level I)
- There are insufficient data on the value of prophylactic diet in infancy, but breast feeding is supported and the delayed introduction of egg and fish till the age of 1 in atopic families (Level III).

Psychological factors

Psychological factors are of considerable importance in eczema. Significant eczema makes life hard from infancy to till adult life. Settling in at school is harder if eczema is troublesome. Growing up and passing through puberty is harder if eczema makes you look different. Conversely, when life is a struggle, the stress may be manifest as eczema. Family dynamics may distort as a result. Intervention in the form of continued support within families education is most effective if the parents feel in control and optimistic as a result.

Second-line treatments

Ultraviolet "light"

Ultraviolet radiation (UV) has been demonstrated to be an effective therapy for adult atopic eczema [3] (level IB) though the response rate and duration of remission are not as good as those for psoriasis (level IV). There are limited data on the use of ultraviolet light in eczema in children. The mode of action is likely to be immunomodulatory and anti-microbial. The precise therapeutic action spectrum for atopic eczema is unknown .

- Broad band UVB (290-320nm) [81], combined UVA and UVB [82] and narrow band UVB (311nm) [83] are effective for moderately severe eczema which is not sufficiently improved by emollients and topical steroids (level IB) although long term remission is unlikely to occur. Combined UV A/B therapy has been shown to be more effective than broad band UVB alone in comparative studies [82] (level IB) but there is no published experience of its use in children. Narrow band UVB has been shown to be an effective adjunctive treatment for adults with atopic eczema in a randomised controlled trial [83]. In addition, using an air conditioned unit, it has been shown to be a useful therapy in children with atopic eczema in an open study [84]. High dose UVA1 (340-400 nm) has been shown to be to be a successful monotherapy for the treatment of an acute exacerbation of atopic eczema [85] (level IB).

- PUVA is an effective treatment for atopic eczema in children and adults [86, 87] (level IIB). Treatment with PUVA has been recommended for children over the age of 10 years with severe widespread eczema unresponsive to other forms of therapy (including UVB) and associated with substantial physical, psychological, educational and social disability [87] (level III). Clearance rates of 74% are described with remission achieved in 60% following gradual reduction in frequency of treatment. Long term remission (>12 months) was reported in 41% of patients. However, this required prolonged treatment with a very high number of exposures and total cumulative dose. It is the consensus view that PUVA does offer benefits in severe eczema but these benefits are often short lasting (level IV) and need to be balanced against the risk of long term side effects, particularly in children. Oral Prednisolone may be required in the early stages of treatment to allow an increase in the dose of UVA used (level IV).

- Minimal erythema dose (MED) and minimal phototoxic dose (MPD) testing is recommended for narrow band UVB and PUVA respectively (grade B/levelI IIb) as there is poor correlation between skin type and MED and MDP response (75,76).

Risks associated with phototherapy

- Erythema and burning are short term adverse effects of all types of phototherapy
- The doses of UVB received during phototherapy for atopic dermatitis are generally much lower than for the treatment of psoriasis but there are no data to actively quantify the risk of skin cancer from UVB in these patients.
- There are no data on the long term risk of skin cancer in eczema patients treated with high numbers of PUVA exposures. This can only be extrapolated from psoriasis patients who are generally from an older patient population.
- Eye damage: atopic cataracts are rare having their peak age at 15 to 25 years (level IV). They may be rapidly progressive. Young people beginning PUVA therapy should have their eyes examined by slit lamp prior to beginning therapy to exclude the presence of an early cataract.
- There may be an early flare and some use oral steroids to moderate the risk of such a flare (level IV).

- Eczema herpeticum may occur during PUVA and UVB therapy especially if steroids are given by mouth concurrently (level IV).

Recommendations

- UV therapy is effective in the treatment of eczema but generally has a short term rather than a long term effect (Grade A/ level 1B)
- Narrow band UVB is more effective than broad band UVB (grade B/level IIB)
- PUVA can offer additional benefits in severe eczema unresponsive to other forms of therapy including UVB (grade B/level IIB)
- MED/MPD testing is recommended for UVB and PUVA treatment respectively (Grade B/ level III).
- Caution should be exercised in using UV treatment in patients with a history of eczema herpeticum (Grade B/ level III)
- Eye examination should be carried out in atopics prior to PUVA treatment to ensure that atopic cataracts are not already developing (Grade B/level IV)
- The practicalities of treatment mean that light therapy is prohibited in the very young
-

Immunosuppressants

A tiny proportion of patients with severe disease will not respond to standard therapy and may benefit from oral immunosuppressant therapy.

Oral steroids

Oral Steroids may be useful in severe disease to interrupt the vicious cycle effect but overall oral steroids are of very limited value in eczema.

- Growth may be inhibited by oral steroids in childhood and therefore should probably be avoided in those less than 2 years old and greater than 11 years until after puberty as these are the times of maximal growth [88]. Eczema itself, however, also inhibits growth.
- Brief courses, as used to good effect in the treatment of asthma, are not always helpful in atopic eczema [89]. Similarly relatively high doses are initially required to gain control i.e. 1 to 1.5mg/kg.
- Patients often relapse quickly following cessation of the steroids and tailing off the dose is important.

The steroids should be given as a single daily dose early in the morning and alternate day dosing contemplated.

Cyclosporin

Cyclosporin should be reserved for those suffering from severe, long-standing atopic eczema resistant to other therapies, and causing the patient significant suffering and disability. It has been used successfully to treat troublesome eczema in children as young as 15 months old with on average good responses in greater than two-thirds of severely effected children. Indeed the efficacy of cyclosporin in children is on a par with its good effect in adults which has been shown in several trials [90-95].

The dosage used in children has ranged from 1 to 5 mg/kg and is usually highest while treatment is being established. Once control has been gained the lowest dose providing adequate disease control should be sought. Twice daily administration is recommended. The duration of therapy has also varied. Two strategies have been reported [96]:

1. Short term therapy for 6 to 12 weeks.
2. Longer term therapy for up to and beyond a year.

There are advantages and disadvantages of both strategies but in general the approach taken should be tailored to each patient's individual needs according to the experience of the clinician.

Cyclosporin for use in children comes in a solution which can be mixed with orange juice/squash, apple juice or water (but not grapefruit juice) to aid compliance.

Advantages of cyclosporin :

- Rapid clinical improvement frequently by 2 weeks of therapy.
- Especially good at relieving the itch of atopic eczema.
- Long-term remission reported in some adults following cyclosporin.
- Standard therapy can continue e.g. topical steroids.
- Aggressive treatment in theory should help reverse some of the complications of atopic eczema e.g. growth retardation.

Disadvantages of cyclosporin :

- Minimal effective dose higher than that usually needed to treat psoriasis

- Most patients relapse once treatment is stopped (50% in first 2 weeks following cessation, >90% by 6 weeks). However usually the relapse is to a less severe state than the pre-treatment level and can be adequately controlled by topical treatments not previously effective.
- Serious side-effects i.e. nephrotoxicity
- Need for monitoring
- Live vaccinations should be avoided during therapy

- Herpes simplex infections should be allowed to clear prior to starting treatment. Similarly any S Aureus skin infection should be treated but is not a contraindication to starting cyclosporin.

Erythromycin should be avoided in treating infections in patients on cyclosporin because of its effects on blood levels.

Side-effects
Generally the treatment is well tolerated. Patients should however be warned of the theoretical increased risks of lymphoma and squamous cell carcinoma if long-term treatment is contemplated or expected. Cyclosporin itself is not thought to be directly carcinogenic but malignancies appear to be a complication of immunosuppression itself. The absolute risk is not known and is likely to be less than for those immunosuppressed for transplant purposes. Previous immunosuppression with other agents (e.g. steroids, methotrexate) and past UVB or PUVA may increase this risk and should be taken into account when making the decision whether to start cyclosporin or not. Whether these risks apply if only short term therapy is used is unknown.

Azathioprine

Azathioprine has been used for many years in severe atopic eczema [97]. Its more frequent use has been principally limited by the occasional but regular occurrence of potentially dangerous myelosuppression. However, it is becoming clear that with standard dosage, myelosuppression mainly in those who have low levels of thiopurine methyltransferase (TPMT), s an important enzyme in the metabolism of azathioprine and 6-mercaptopurine. 88.6% of the normal population are homozygous for an allele for high TPMT activity; about 0.3% are homozygous for low-activity TPMT alleles, leading to effective absence of TPMT activity and high risk of severe myelosupporession if given even low doses of azathioprine. The remaining 11.1% are heterozygotes, leading to a relatively increased risk, though as this enzyme appears to be induced by exposure to the drug, it may be reasonable to introduce it carefully at a low dose. However, it may be wiser to avoid using the drug in those who do not have normal erythrocyte TPMT levels on initial testing, ie about 1 in 9 of the population.

In those with normal erythrocyte TPMT levels, the use of azathioprine appears to be very safe, the principal adverse effects in this population being occasional nausea and diarrhoea, and, uncommonly, a hypersensitivity syndrome featuring jaundice, maculopapular exanthems and flu-like features such as malaise, pyrexia, arthralgia and myalgia are prominent.

There is probably little increased risk of infection in patients treated with azathioprine if this is not combined with prednisolone. The manufacturers advise that live virus immunisations should be avoided in those receiving azathioprine, and that the response to certain other immunisations may be blunted.

A proportion of patients develop hepatitis on this drug.

There are data suggesting increased risk of malignancy from long-term use of azathioprine [98-100]. The risk is difficult to quantify, but one study suggested as much as 12-fold increase in non-Hodgkin's lymphoma and a 5-fold increase in squamous carcinoma, albeit in a renal transplant population [101].
The availability of testing for blood TPMT levels, and concern about the toxicity and cost of cyclosporin have led to a re-evaluation of azathioprine as a treatment for severe atopic eczema both in adults and children. The optimal dose for treating atopic eczema probably lies between 2.5-3.5 mg/kg/day. There appears to be a delay of between 4-8 weeks in the onset of the therapeutic effect.

Monitoring
Prior to starting treatment, blood should be taken for an erythrocyte TPMT level. This is not yet widely available but is undertaken at low cost by the Purine Research Laboratory, 5th Floor, Thomas Guy House, Guy's Hospital, London SE1 9RT: (tel Guy's ext 4024). Routine clinical chemistry should be undertaken for renal and hepatic function, and a full blood count should be done. Azathioprine can be started at a therapeutic dose in those with a normal TMPT level; there is no need to start at a low dose [102]. Short courses are not effective, and treatment will need to be given for a period of 1-2 years if there is to be a reasonable chance of withdrawing treatment without substantial recurrence. The most appropriate frequency for on-going monitoring during treatment is not established, but it is probably wise to repeat the full blood count and routine clinical chemistry after 4-6 weeks of starting treatment and at least 3 monthly thereafter.

Prolonged remission following a course of azathioprine has often been reported and patients can require fewer antibiotic courses, decreased amounts of potent topical steroids and less hospital admissions.

In summary, the indications for the use of azathioprine in atopic eczema are the same as that for cyclosporin, although there are no formal clinical trials to back up the use of azathioprine in children. The choice of which of these two drugs to use will depend to a large extent on the clinician's own preferences and experiences.

Methotrexate

There is a single retrospective report of the use of methotrexate in adults with eczema [103]. This is of interest, but the data are so sparse that its use cannot be supported.

Cyclophosphamide

This has been used in doses of 100mg daily in adults with apparent success. However cyclosporin and azathioprine would seem to be preferable.

Recommendations

- Oral immuno-suppressants are rarely needed to control severe eczema.
- Oral steroids may be useful, occasionally in the short term but should be tailed off more slowly than in asthma to avoid relapse (Grade A, level III). They should probably be avoided under the age of 2 and around puberty in order to minimise the deleterious effects of oral steroids in growth inhibition (Grade A, level III).
- Cyclosporin is effective in eczema used twice daily and is given at a dosage of 1 to 5 mg/kg per day (Grade A, level I). Use requires the monitoring of blood pressure and creatinine levels as nephrotoxicity is the principal side-effect of therapy.
- When cyclosporin is stopped relapse is usual although the eczema may then be less severe: cessation should be gradual to reduce the risk or rebound (Grade A, level I).
- Azathioprine is effective in some patients with severe eczema. Some people develop hepatitis on the drug and long term anxieties relate to an increased risk of cancer (Grade B, level III). Rarely precipitous marrow depression occurs after azathioprine

Chinese herbal medicine

This treatment is considered occasionally when the dermatologist is faced with a patient with widespread eczema refractory to all conventional therapy. Traditional Chinese practitioners use individual formulations containing several plants. There have been no reliable trials. There are however multiple reports of problems including liver toxicity, cardiomyopathy, heavy metal contamination and undisclosed steroids in herbal creams.

Problems of treatment

- unpalatability
- preparation time
- occasional hepatotoxicity

The only formal studies carried out have used a standardised ten herb preparation produced by Phytopharm [104, 105]. In a placebo controlled trial the treatment was shown to be well-tolerated, with active treatment being superior to placebo. The product is however no longer available for clinical use.

Gamma-linoleic acid (Evening primrose oil)

Patients with eczema have an increase in linoleic acid and a decrease in its metabolites: [gamma-linolenic acid (GLA), dihomogammalinolenic acid (DGLA) and arachidonic acid (AA)] suggesting a defect in the delta-6-desaturase enzyme (D6D) [106-108]. Oral treatment with GLA may increase the levels of D6D metabolites of linoleic acid (LA) and it was suggested that it may improve the clinical symptoms of atopic eczema. Some plants rich in GLA are known. Evening primrose oil (Epogam) consists of 8.9% GLA, 6.8% palmitic acid, 7.7% oleic acid and 74.7% LA. Epogam is of controversial benefit in atopic eczema. Many trials have been done and a meta-analysis of 9 studies has shown an improvement in atopic eczema in parallel studies ($p<0.0001$) in terms of the degree of inflammation, dryness, scaling and overall severity of the eczema. No clear cut improvement, apart from the degree of itching noted, could be demonstrated in trials with a cross-over design[8]. In some trials, levels of DGLA and AA were determined in addition to clinical evaluations and a positive correlation was seen between and increase in DGLA and AA and clinical responses[8-13]. In none of the studies were unwanted effects observed.

A recent review of the history of this agent leading to loss of its licence was published in the BMJ[109].

Recommendations

- Chinese herbal medicine (as a commercial extract called Phytopharm which is no-longer available) has been shown to be more effective than placebo (Grade B, level II). Traditional herbal medicine has reported toxicity. It is recommended that patients should be cautioned against the potential risks of its use and that their liver function tests should be monitored.

There does not appear to be sufficient evidence to support the use of evening primrose oil in eczema (Grade B, level 1) indeed the drug has now lost its product licence in the UK.

The future

Atopic eczema is mediated by the immune system, and immuo-modulatory treatment is the hope for the future [110]. There are some data, which suggest that modulation of Th1/Th2 responses may induce resolution of eczema [111] and some evidence that early BCG vaccination may have a protective effect [112], so that phase ii randomised clinical trials of killed mycobacterium vaccae immunisation are in progress in children aged 5 to 16 years.

Recently oral viable bacteriotherapy with probiotics has shown very encouraging results [113]. Probiotics are non-pathogenic micro-organisms such as Lactobacilli[114] which are thought to have anti-inflammatory and anti-allergic effects [115]. A double-blind placebo controlled crossover study showed a therapeutic effect of Lactobacilli by mouth in children with atopic eczema [116].

Appendix 1 THE CONSENSUS GROUP

This document on 'atopic eczema management guidelines' has been developed with input, initially by experienced medical and nursing staff from Yorkshire and surrounding areas (NHS Northern and Yorkshire region). It has also benefited from the input of national opinion leaders with experience in managing atopic eczema who attended an advisory board meeting to develop the guidelines. The key members of the advisory board were;

Dr David Atherton	Consultant Paediatric Dermatologist Great Ormond Street Hospital for Sick Children, Great Ormond Street, London WC1N 3JH
Professor Tim David	Consultant Paediatrician, Booth Hall Children's Hospital Charlestown Road, Blackley, Manchester M9 2AA
Dr Rosemary Lever	Consultant Dermatologist, Glasgow Royal Infirmary 84 Castle Street, Glasgow G4 0SF
Dr Sue Lewis-Jones Dr Jonathan O'B Hourihane	Consultant Paediatric Dermatologist, Dundee Senior Lecturer, Infection, Inflammation and Repair Division, Assistant Director, WellcomeTrust Clinical Research Facility Mailpoint 218 Southampton University Hospitals NHS Trust Tremona Road, Southampton SO16 6YD

The following contributed to development of the guidelines by contributing to an open meeting on eczema which was the beginning of the guidelines- Dr Susanna Baron, Leeds, Dr Gordon Ford, Dewsbury, Dr Dominic Smith, Leeds. Dr Keith Brownlee, Leeds, Dr Jonathan Darling, Leeds, Dr Richard Pumphrey, Manchester, Dr Sabine Sommer, Leeds, Dr Elizabeth Potts, Halifax, Ms Kirsten Tremlett, Leeds, Dr Paddy McLean, Leeds, Dr Phil Wood, Prof K T.Holland and Dr R Bojar.

Dr Graeme Stables, Leeds, Prof Bill Noble, Dr Barbara Dodman, Pontefract, Dr Darren Seukeran, Cleveland, Dr Anne Myatt, York, Dr Martin Schweiger, Leeds, Dr Derek Barker, Bradford, Miss Edi Balodis, Leeds, Dr Rachel Wachsmuth, Leeds, Dr Caroline Wilson, Leeds, Dr Catriona Henderson, York, Dr Kathryn Thomson, Leeds, Dr Sue Macdonald-Hull, Pontefract, Dr Annette Murphy, Hull, Dr Aileen Taylor, Newcastle, Dr Bruce Pollock, Leeds, Dr Mike Cheeseborough, Huddersfield, Dr Allan Highet,York, Dr Alison Layton, Harrogate, Dr Gabriella Rieberer, Bradford, Miss Mercy Jeyasingham, National Eczema Society, Dr Kate Hammond, Harrogate, Dr John Preshaw, Bradford.

Useful Addresses

Anaphylaxis Campaign
PO Box 149
Fleet
Hampshire
GU 139XJ
01252 542029

Medic Alert
17 Bridge Wharf
156 Caledonian Road
London
N1 9RD
0171 833 3034

National Eczema Society
163 Eversholt Street
London
NM1 1BU

Acaracides may be obtained from
Crawford Chemicals
Denbigh House
Bletchley,
Milton Keynes
MK1 1YP

Medivak, suppliers of specialist vacuum machines
Bollin House,
Riverside Works,
Manchester Road,
Wilmslow,
Cheshire,
SK9 1BJ

For patient directed information on allergy this web site is valuable.www.rcpath.org (PATIENT SECTION)

Appendix: Leeds PAEDIATRIC ANAPHYLAXIS KIT INFORMATION SHEET

This sheet is to be used in conjunction with an Anaphylaxis Kit prescribed by a Paediatrician and obtained from the Hospital Pharmacy. You should receive instruction in its use from an appropriate person, such as the prescribing doctor or clinic nurse.

1.1 Introduction to the Kit

Your child may be at risk of having a severe reaction of a type called "Anaphylaxis". This can occur in response to certain foods, drugs, or insect stings, and can even be fatal. Fortunately, the correct treatment given early is very effective. It is therefore vital that parents, carers and schoolteachers know:

- that your child could have such a reaction and how to recognise it;
- that treatment needs to be given early, and how to give the treatment;
- what might provoke the reaction, so that it can be avoided if at all possible.

The Anaphylaxis kit contains those drugs necessary for early treatment of an attack. Children with food allergies should be taught avoidance measures, such as reading food packaging, and enquiring about food ingredients when eating away from home.

1.2 Recognising an Anaphylactic reaction

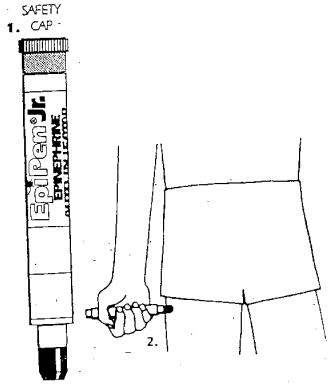
Symptoms may occur within minutes of exposure. Early warning signs for a severe reaction include itching of the skin, a raised rash (hives), flushing, swelling of the tissues of the lips, throat, tongue, hands and feet. As the reaction progresses, there may be wheezing, shortness of breath, coughing, hoarseness, headache, nausea, vomiting and abdominal cramps. The child may appear pale, sweaty and restless. There may then be loss of consciousness and collapse. In a mild reaction, there may be a rash and skin redness, a high temperature, and sickness and diarrhoea.

1.3 Contents of The Kit

Two Epipens (injectable adrenaline)
Steroid tablets (Prednisolone) which dissolve in water.
Antihistamine syrup (Chlorpheniramine)

1.4 The Epipen

The most important part of treatment is to give an injection of adrenaline. Once it is clear that the child is having a reaction, this needs to be given as early as possible. For this reason you have been provided with a Kit containing two injection-pens called Epipens. The Epipens should be stored at room temperature (do not refrigerate). They are light sensitive, and so should be kept in the tube provided. They should be checked periodically to ensure they are still in date, that the solutions are not discoloured, or cloudy.



1.4.1 Directions for Use

1. Pull off the grey safety cap
2. Place black tip on the outer thigh, at right angle to leg (illustration 2.). (Always apply to thigh).
3. Press hard into thigh until the Auto-injector clicks, and hold in place for 5-10 seconds. The Epipen unit should then be removed and discarded. Massage the injection area for 10 seconds.

2.0 WHAT TO DO IF YOUR CHILD IS HAVING AN ANAPHYLACTIC REACTION

Have they got any of the following?

- Swollen face, mouth, throat or tongue
- Difficulty breathing or wheeze
- Lapsing into unconsciousness
- Sudden collapse

YES

▼

SEVERE REACTION

1. Remove the cause of the reaction if possible (eg sting, food, drug).

2. Give Epipen injection into thigh (see instructions).

3. Dial 999 for ambulance: tell them your child is having an anaphylactic reaction.

4. If child conscious and able to swallow give:

   ____ mls of Chlorpheniramine liquid.

5. If no improvement after 10 minutes, give the second Epipen injection.

Have they got any of the following?

- Itchy skin or rash
- Diarrhoea or vomiting
- Colicky tummy ache
- High temperature

YES

▼

MILD REACTION

1. Remove the cause of the reaction if possible (eg sting, food, drug).

2. Give ____ mls of liquid Chlorpheniramine

3. Contact your GP or go the Accident and Emergency Department.

If the reaction becomes more severe, or if you are not sure if it is mild or severe, give the Epipen and dial 999.

Further information may be obtained from:

The Anaphylaxis Campaign
PO Box 149
Fleet
Hampshire
GU13 9XU

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