Recent developments in the treatment of childhood atopic eczema

ABSTRACT—Even with the most careful application of conventional treatment, atopic eczema can be a disabling handicap in severely affected children. In refractory cases the conventional therapeutic options—potent topical steroids or the use of systemic steroids—are potentially hazardous and associated with relapse after therapy has been discontinued. The main drawbacks to recent experimental approaches, such as oral cyclosporin, photochemotherapy or interferon-γ, are relapse after cessation of therapy and potentially serious side-effects. Avoidance of certain foods, pets and house dust mites is an option, the major drawbacks being the lack of tests to identify triggers or predict response, and the possible nutritional or psychological hazards of elimination diets. Difficulties with these approaches emphasise the need for close attention to the details of conventional treatment.

In its severe form, atopic eczema is a disabling childhood handicap (Fig. 1). It is often poorly managed and has attracted many scientifically ill-founded treatment practices both within conventional medicine and beyond. Even with the most careful application of conventional treatment of atopic eczema in childhood [1] (see Table 1), some children continue to suffer from intractable and handicapng eczema. This article reviews existing and new approaches to these difficult cases, under the major headings of steroids, diets, immune manipulation, and a miscellaneous assortment of other therapies.

Steroids
The judicious use of topical steroids is currently the single most useful form of treatment of atopic eczema. Fear of using safe, mildly potent, topical steroids is a cause of much needless suffering. To avoid this, any prescription should be accompanied by an explanation of the different steroid potencies [2].

Potent topical steroids
The main hazard of regular use of potent topical steroids is skin atrophy, which can be particularly disfiguring on the face, and irreversible striae which most often appear on the inner thighs. Although most children with atopic eczema are adequately treated with mildly potent (British National Formulary category IV [3]) steroids (eg 1% hydrocortisone ointment), it is common in older children to see refractory, heavily lichenified patches of eczema confined to the front of the knees, the wrists, and the ankles, and here it makes no sense to withhold a category III or II preparation because of fear of skin atrophy. The situation is less easy when there are widespread areas of severely inflamed lesions; the price for undertreatment is disfigurement and handicap, and the penalty for overtreatment with potent steroids is similar. A further problem in the treatment of widespread skin lesions is the risk of percutaneous steroid absorption resulting in adrenal suppression and growth stunting. The lack of any validated guidelines as to what constitutes a safe daily dosage of topical steroids in relation to age, surface area, or steroid potency is a real problem when trying to steer a course between under- and overtreatment.

Systemic steroids
The short-term (one- to two-week) use of systemic steroids (eg prednisolone) is generally unhelpful because of relapse following steroid withdrawal. Parental elation is followed by even greater gloom. However, there is clearly a small number of children who are so severely handicapped (eg unable to attend school) because of refractory atopic eczema that long-term systemic steroids are justifiable [1], although there is the contrary view that even where life is intolerable systemic steroids should be withheld on the grounds that the disease is not life-threatening. Unfortunately, these particularly difficult cases often require high and potentially growth-suppressant daily doses to achieve control, leaving little scope for a more preferable low-dose, alternate-day, growth-sparing regimen. As far as trying to minimise growth suppression is concerned, if alternate-day therapy is not possible, it makes sense to try and give prednisolone as a single daily dose early in the morning. Controlled trials have not been performed, but one would not expect treatment with growth hormone to overcome growth stunting due to steroid therapy. Once established on systemic steroids, the management consists of repeated attempts to reduce the dose and keep it to a minimum, aiming to wean the patient off altogether within 6 to 12 months if possible. Longer treatment may be required. As with potent topical steroids, striae are a rare but unsightly complication (Fig. 2).
Before embarking on long-term oral steroids, there is a rationale for trying a regimen of oral plus inhaled beclomethasone dipropionate rotacaps in a total daily dose of up to 1200 mcg per day. The efficacy of this regimen has been demonstrated in a double-blind placebo-controlled trial [4], and the adverse effects are minimised partly because of the very short serum half-life of beclomethasone, and partly because most of the swallowed drug is deactivated in the liver before reaching the systemic circulation.

Dietary elimination

There have been no double-blind or randomised studies in children with atopic eczema comparing dietary therapy with other treatment. Without such studies it is impossible to tell whether or not any benefit from diets is due to a placebo effect, whether the benefit is temporary (lasting until the child would have grown out of the disease anyway), or whether such treatment actually influences the ultimate prognosis by shortening the duration of the disease. There are, however, several studies in which children with atopic eczema improved on an elimination diet, and were then given food challenges to confirm or refute intolerance to individual foods. The drawback to this design is that double-blind food challenges can confirm the presence of food intolerance but do not establish how much improvement is due to food avoidance and how much is attributable to a placebo effect.

The fundamental strategy of the dietary approach is to eliminate one or more foods for a defined period of time (eg six weeks), with supervision by a dietitian to ensure that relevant foods have been fully avoided and that the resulting diet is nutritionally adequate [5]. If the diet is unsuccessful it is abandoned, but if it has been beneficial it is continued, and single foods reintroduced about once a week. Skin-prick tests and radio-allergosorbent (RAST) tests are not helpful because of the high rate of false positive and false negative results. In practice three types of diet can be used. All include avoidance of known or suspected food triggers plus a selection of two or more other foods.

Cow’s milk protein and egg avoidance

Trials of this treatment have given conflicting results. Its main virtue is simplicity rather than efficacy. Failure may occur because the child is not intolerant to these foods, because the foods were incompletely avoided, or because of failure to eliminate other trigger foods.

Few foods diet

This consists of exclusion of all foods except for five or six items. Such diets comprise a meat (usually lamb), three vegetables (for example potato, rice and carrot or a brassica—cauliflower, cabbage, broccoli, or sprouts), a fruit (usually pear) and possibly a breakfast cereal (for example Rice Crispies). The value of this diet has been called into question by a recent study which showed improvement after six weeks, but when patients who had improved were compared with those who failed to improve or those who failed to comply with a diet, the results at 12 months showed that all three groups were greatly and equally improved [6].

Elemental diet

The application of an inpatient regimen of four to six weeks of a so-called elemental diet (eg Vivonex (Tol-erex) Standard*) is the ultimate test of whether food intolerance is relevant or not, but there are no controlled data on the value of this approach. Local experience of treating 40 exceptionally severely affected patients in this way indicates that it can offer a solution

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*Available from Norwich Eaton Pharmaceuticals Inc, 17 Eaton Avenue, P.O. Box 231, Norwich, NY 13815, USA.
Table 1. Conventional treatment for atopic eczema

| Dry skin                  | Reducing damage from scratching | Night sedation          | Topical steroids          | Infection                  |
|---------------------------|--------------------------------|-------------------------|---------------------------|---------------------------|
| Emollients for dry skin at bath time | Keep nails short and file daily with emery board | Sedating antihistamine (eg trimeprazine) at bedtime | Mildly potent topical steroid ointments (eg 1% hydrocortisone) | Oral antibiotics (eg flucloxacillin) for skin infection |
| Reduction or increase in frequency of baths | Wear mittens made from cotton tubular bandage at night | | Topical steroid-antiseptic combination ointments | Antiseptic in bath water for recurrent infections |
| Dispersible bath oil | Distraction | | | Prevention of secondary infection in herpes skin infections |
| | Gentle rubbing of skin by parent | | | Intravenous acyclovir for serious initial infections with herpes simplex virus |


to certain cases, the major drawbacks comprising the lack of a guarantee of success (30% failure rate), family disruption associated with two to three months hospitalisation, weight loss, hypo-albuminaemia, and loose stools due to hyperosmolarity of the elemental formula [7].

Immune stimulation or suppression

The association of atopic eczema with abnormalities of a number of immunological measurements, most notably the marked elevation of the serum IgE concentration, points to an underlying immunological basis for the disease.

Cytotoxic agents and antimetabolites

There are anecdotal reports, reviewed elsewhere [8], of clinical improvement of atopic eczema in adults during therapy with cyclophosphamide, aminopterin, nitrogen mustard, thioguanine, and azathioprine, but fears of bone-marrow toxicity, lymphoma production and sterility, and the return of active disease after stopping treatment, have deterred studies of these agents in children. Cyclosporin and interferon are discussed separately below.

Oral cyclosporin

In an open study of adults with refractory atopic eczema, cyclosporin was given in an average dose of 4 mg/kg/day for one to 31 months, and a good response was reported in 10 out of the 13 patients [9]. However, fears of renal toxicity and lymphoma production, and the return of active disease within three weeks of stopping treatment [10], have deterred further studies in children, and the place of oral cyclosporin in the treatment of atopic eczema in childhood is uncertain.

Topical cyclosporin

Topical cyclosporin in the form of a 10% gel appears to have poor penetration into the skin, and in a double-blind placebo-controlled trial only 10 out of 18 patients (aged two to 29 years) responded to twice-daily treatment [11]. A burning sensation after application was a common problem. The results of further studies are awaited.

Interferon-γ

In an open study of 22 patients with atopic eczema and raised serum IgE levels, daily subcutaneous injections of recombinant interferon-γ in doses of 0.01–0.1 mg/m² were associated with clinical improvement, which was followed by relapse within three days of stopping therapy [12]. There was no control group in this study, so it is impossible to tell whether the benefit was due to the drug or a placebo effect. The temporary nature of the improvement and the need for
injections makes this unlikely to be a popular treatment for children with atopic eczema.

Thymopentin

Thymopentin is a synthetic pentapeptide corresponding to the amino-acid residues 32 to 36 of the linear 48 amino-acid sequence of human thymopoietin. A randomised double-blind placebo-controlled study of thymopentin, given as daily subcutaneous injections for six weeks to 48 patients with atopic eczema aged from two to 66 years, has recently been reported [13]. Both the placebo (saline) and thymopentin treated groups demonstrated a progressive and statistically highly significant decline in the severity of their disease, but the reduction of disease severity in the thymopentin-treated group was significantly greater than in the placebo group. Further investigations are needed to determine whether thymopentin acts by correcting the immunological abnormalities described above, and to see whether it has any place in the treatment of atopic eczema.

Thymostimulin

The observation that a deficit of T-lymphocytes in atopic eczema could be corrected after incubating them with a calf thymus extract, thymostimulin, led to a double-blind placebo-controlled study [14]. Thymostimulin 1.5 mg/kg was given twice weekly. Circulating CD8+ lymphocyte levels returned to normal, and treatment was associated with clinical improvement, although this did not reach statistical significance.

Transfer factor, bestatin, colchicine, levamisole

These agents have no clinical benefit in atopic eczema [8].

Sodium cromoglycate

Efforts to improve the smooth muscle relaxant action and reduce toxicity of khellin, a naturally occurring furanochrome, led to the synthesis in 1965 of the sodium salt of a bis-chromone carboxylic acid, sodium cromoglycate. Although cromoglycate inhibits mediator release from mast cells, this does not explain all its effects.

Topical sodium cromoglycate

An early study of 10% cromoglycate ointment in children with atopic eczema seemed to show a beneficial effect, but further studies of the 10% cromoglycate ointment and a 4% cream have failed to demonstrate improvement [15]. One other study of 4% cromoglycate cream suggested that the benefit was confined to mild cases [16].

A recent double-blind study of 45 patients under the age of three years reported dramatic benefit after the daily application of a 1% cromoglycate nebuliser solution [17]. The improvement claimed is in stark contrast to previous studies, and this plus the methodological drawbacks (an unusual scoring system which took no account of the extent of the disease, and a lack of information about how the solution was applied) means that this approach is unlikely to be taken up unless supported by further data.

Oral sodium cromoglycate

The entry of ingested food antigens into the circulation may be increased in patients with atopic eczema, and there are anecdotal reports of diminished antigen entry and reduced symptoms after oral administration of cromoglycate. This has been the basis for a number of clinical trials of oral cromoglycate, the results of which have been generally negative [18]. Paradoxically, oral cromoglycate may cause marked worsening of symptoms [19], although the mechanism for this is not known.

Nedocromil sodium

Nedocromil sodium has a similar action to sodium cromoglycate. Studies of oral nedocromil in adults with atopic eczema [20], and topical 4% nedocromil cream in children and adults with atopic eczema [21], failed to show any benefit.

Phosphodiesterase inhibitors

Hanifin has shown that an elevated leukocyte cyclic AMP phosphodiesterase (PDE) accounts for the low intracellular cyclic AMP levels found in atopic eczema and correlates with abnormal functional parameters such as increased basophil histamine release and in vitro IgE synthesis [22]. He has suggested that there may therefore be a basis for the use of short courses of oral theophylline, a PDE inhibitor, although no trials of this treatment have been published. Caffeine, another PDE inhibitor, has been tried in various topical formulations, apparently with little benefit [10,23]. A third PDE inhibitor, papaverine, is without benefit when given orally [24].

Phototherapy and photochemotherapy

Ultraviolet (UV) radiation

UVB, sometimes combined with UVA, has been successfully used in the treatment of adults with atopic eczema [25]. The mode of action of UV radiation is uncertain. The combination of UVB and UVA appears to be slightly more effective in producing remissions, and is somewhat less likely to be followed by relapse after cessation of therapy [26,27]. Drawbacks to this
approach which are likely to deter its use in childhood atopic eczema are the almost inevitable relapse following treatment, skin ageing (solar elastosis and wrinkling), and the long-term increased risk of skin cancer.

Psoralen photochemotherapy (PUVA)

Fifteen children with severe atopic eczema were given psoralen 0.6 mg/kg two or three times a week, and treated with UVA at 1 J/cm², with the UVA dose gradually increased by increments of 0.5–2.0 J/cm² at intervals of not less than one week, depending upon skin tolerance and response [28]. Fourteen of the 15 patients achieved almost complete clearance of skin lesions, which took 10–25 weeks (median 16 weeks). Major deterrents to PUVA therapy for atopic eczema in childhood comprise severe irritation requiring systemic steroids, relapse after treatment, and the increased risk of skin cancer and possibly cataract formation [29].

Miscellaneous other approaches

Evening primrose seed oil

Oil extracted from the seeds of the evening primrose (Oenothera biennis and lamarkiana) is a rich source of polyunsaturated fatty acids of the ω6 type, including gamma-linolenic acid (GLA). Its GLA content has made evening primrose seed oil (EPO) a fashionable but unproven treatment for an assortment of disorders which include schizophrenia, multiple sclerosis, cancer, and arthritis. Wright and Burton administered EPO capsules (each containing 360 mg of linoleic acid and 45 mg of GLA) to 60 adults and 39 children with atopic eczema, in a dose of one to six capsules twice daily, in a 12-week double-blind cross-over study [30]. There was little benefit from low-dose treatment (four capsules per day), and children were not helped, but adults receiving 12 capsules per day had a significantly improved symptom score. Subsequent studies have given conflicting results. The manufacturers of EPO conducted a meta-analysis of nine selected studies [31], and this claimed to show significant benefit from oral EPO, although this analysis has been severely criticised [32], not least on the grounds that it failed to include the largest single study of EPO in which no benefit was seen [33]. It seems highly doubtful that EPO is of any benefit in mild or severe cases of childhood atopic eczema.

Fish oil

As with EPO, fish oil is being promoted for a wide range of conditions such as arthritis, asthma, psoriasis, and the prevention of coronary thrombosis. A commercially available extract of fish oil contains large amounts of polyunsaturates of the ω3 type, including eicosapentaenoic acid (EPA), a precursor of eicosanoid synthesis. A double-blind placebo-controlled study of this fish-oil extract given by mouth to 31 adults with atopic eczema showed significant improvement of patients’ assessment of symptoms but no significant improvement of the physicians’ assessment scores [34]. On this evidence, fish oil does not appear to be indicated for atopic eczema.

Zinc

Oral supplements of zinc salts have become popular remedies for a range of unrelated disorders, and have been specifically recommended for the treatment of atopic eczema. Although skin lesions are an important feature of zinc deficiency, these lesions do not usually resemble those of atopic eczema. The plasma concentration of zinc is normal in atopic eczema [35], but laboratory measures of tissue zinc are imperfect indicators of zinc deficiency. It is accepted that the ultimate test of zinc deficiency is a clinical response to zinc supplementation: this is currently under investigation.

Selenium

A reduced concentration of selenium in whole blood has been reported in atopic eczema [36], but a double-blind placebo-controlled study of oral selenium 600 mcg daily (in the form of selenium-enriched yeast) failed to show any benefit in 60 adults with atopic eczema [37].

Salbutamol

The β2-adrenoceptor agonist salbutamol, when injected intradermally, inhibits the histamine-induced weal response both in normal subjects and in those with atopic eczema. A double-blind placebo-controlled study of salbutamol ointment (1% base in white soft paraffin) for two weeks in 20 adults with atopic eczema resulted in a significant reduction in the degree of redness but no significant improvement of other clinical features such as pruritus, lichenification, or overall benefit [38]. Oral salbutamol, given as an 8 mg slow-release spandet daily, also failed to result in clinical improvement. It appears that treatment with oral or topical salbutamol is unlikely to help in atopic eczema.

Chloroquine

Although chloroquine was developed primarily as an anti-malarial drug, it has also been used as an anti-inflammatory agent. In an open study, 62 adults with atopic eczema were given chloroquine in a dose of 250 mg per day for three weeks, reducing where possible to 62.5 mg per day, for a total of three to six months [39]. Improvement sufficient to permit withdrawal of topical steroids was seen in 46 patients, though mainly on the highest dosage. Corneal dam-
age, retinopathy, leukopenia, and other side-effects resulted in therapy being stopped in six patients, and this may have deterred further studies.

Ascorbic acid

Preliminary results of a double-blind placebo-controlled study of ascorbic acid (dose unstated) in 10 subjects (age not given) with atopic eczema suggested significant improvement [40]. Better documented studies are necessary.

Chinese herbal remedy

Some patients with atopic eczema have reported benefit from treatment by a Chinese practitioner using a ‘tea’ prepared from a concoction of herbs [41] and a cream for topical application. However, analysis of the cream has revealed a corticosteroid [42], which may account for some of the benefit, although one observer has reported that the major beneficial effect is independent of the cream. As with other herbal remedies, a major concern is hepatotoxicity, and this has been recently described in a nine-year-old girl with eczema who consumed a Chinese herbal tea for six months [43].

Holidays

A striking observation is that the most refractory atopic eczema may improve dramatically or disappear altogether on holiday. A recent study of 300 holidays taken by children with atopic eczema living in the North-West of England found that improvement occurred more frequently (37%) than deterioration (21%) [44]. There was a significant correlation between improvement and a more southerly holiday location; improvement was common in holidays taken in the Mediterranean or further south (69%), while holidays in northern Britain were more likely to be associated with deterioration (27%) than improvement (13%). The cause of the improvement has not been identified, and unfortunately return home is usually followed by relapse.

Hospital admission

Hospital admission may be essential because of a serious complication such as a severe initial infection with the herpes simplex virus. However, a short period of hospitalisation may be useful simply where the eczema is out of control. One approach is to use potent steroids and the application of ‘bodysuit’ bandaging, but neither is suitable for long-term use and relapse following discharge is common and very demoralising for the family. An alternative and perhaps preferable policy is to use admission to establish a simple regimen of therapy which can be continued at home, by finding the best dose of night sedation and applying different topical preparations to different parts of the body and selecting those most acceptable to the patient and the family. The latter is important if non-compliance is to be minimised. A common problem in toddlers is complete refusal of all topical therapy, and a few days hospitalisation can help parents to regain control.

An incidental benefit of admission is for parents to meet others with similar problems, though this can also be achieved by contact with a local branch of the National Eczema Society*.

Discussion

In any child with severe atopic eczema, the first step must be the close attention to details of conventional first-line therapy (see Table 1). Has the role of infection been explored with a trial of anti-staphylococcal antibiotics? Are topical steroids being used adequately? If non-compliance is a major factor, may a short admission be helpful? Is night sedation being given in an adequate dose (eg 50 mg trimeprazine in a three-year or older child)?

The role of elimination diets and avoidance of other allergens such as animal dander and dust mites is controversial. There clearly is a case for this approach when simpler forms of treatment have failed, but the lack of valid tests to identify allergens or predict the outcome of avoidance measures means that this approach has to be in the nature of an empirically based therapeutic trial. Hospitalisation for a so-called elemental diet is a possible last resort.

Where topical therapy and antigen avoidance have failed and the child is seriously handicapped, systemic steroids warrant consideration. In the first instance this should be a trial of oral beclomethasone rotacaps [4]. The major worry of long-term systemic steroids is growth stunting, and this means particularly trying to avoid using them during periods of rapid growth (ie below two or above 11 years). An alternative regimen is photochemotherapy, though this may itself entail the need for systemic steroids, but anxiety about a possible long-term risk of skin cancer is likely to deter parents and doctors.

Other forms of immune manipulation are unacceptable either because of lack of benefit or, more commonly, because of toxicity, although it is possible that an effective and safe formulation of topical cyclosporin may be found in the future. Other agents such as cromoglycate, nedocromil, caffeine, papaverine, evening primrose seed oil, fish oil, zinc, selenium, salbutamol, and chloroquine are either ineffective or toxic.

The discovery of a genetic marker closely linked to the gene for atopic IgE responsiveness [45] means that identification of the atopic gene, its product, and gene therapy are long-term possibilities.

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