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Management of difficult and severe eczema in childhood

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Cite this as: *BMJ* 2012;345:e4770
doi: 10.1136/bmj.e4770

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Childhood eczema is the most common inflammatory skin disease and affects around 20% of children in the United Kingdom.[w1] The condition is also referred to as atopic dermatitis and atopic eczema. The correct nomenclature is debated by experts. The World Allergy Organisation recommends the term eczema, and this is widely used in the UK literature. Atopic dermatitis is perhaps the more accepted term historically and internationally. In this review we will use the term eczema.

Eczema is associated with several comorbidities, including food and respiratory allergies. It has a serious effect on children's and families' quality of life—for example, through sleep disturbance and a negative impact on schooling.[1-3] The resulting impairment in health related quality of life is comparable to that of other chronic diseases of childhood, including diabetes and asthma.[1]

Although mild eczema can often be managed in primary care, around 2% of patients have severe disease that does not respond to topical anti-inflammatory drugs or ultraviolet light treatment alone. These recalcitrant cases require intensive expert management and an individualised approach, especially when systemic immunomodulatory drugs are used. Although these drugs are often life transforming, their side effects require close monitoring. Currently, there is a distinct lack of evidence to help guide the clinician caring for children with severe eczema. This review summarises the management of difficult eczema in primary care, when to refer to secondary care, and treatment options for severe eczema.

How common is childhood eczema?

Eczema is the most common chronic inflammatory disease of early childhood and is often the initial step in the "atopic march," with the subsequent development of food and respiratory allergies (asthma and hay fever).[4]

Eczema affects about 10% of children in the United States and around 20% in the UK.[w2-w4] About two thirds of children with eczema have spontaneous remission before adolescence.[4] The prevalence of eczema has increased in developing countries, especially in urban areas, where populations have adopted a Western lifestyle.[w1 w5]

What causes eczema?

Eczema is a complex disease. Loss of function mutations in the gene that encodes filaggrin (*FLG*), which has a pivotal role in skin barrier function, are strongly linked to the risk of eczema.[w6] Because most cases present in early life and heritability is more strongly linked to the maternal side, environmental influences that operate in utero or in early infancy are probably involved.[w7] For instance, studies have suggested a positive association with water hardness and frequency of washing, as well as exposure to antibiotics in early life.[w7] These influences may be partially due to an effect on the skin microflora, and further research is needed to understand how environmental and genetic factors interact in the development of eczema.[w7] Patients also have well characterised systemic and cutaneous immune abnormalities, including increased total and allergen specific serum IgE; raised cutaneous cytokines, T cells, Langerhans cells, and inflammatory dendritic epidermal cells; and decreased expression of antimicrobial peptides.[w8]

How is eczema diagnosed?

Eczema is diagnosed clinically, usually in primary care. It is characterised by itch, skin inflammation, a skin barrier abnormality, and susceptibility to skin infection.

The disease can be difficult to define because the clinical features vary and presentation depends on age and ethnicity (box 1).[4] It is unclear whether eczema is one disease or whether distinct subphenotypes have different genetic and immunological profiles.

A systematic review concluded that the UK refinement of the Hanifin and Rajka diagnostic criteria is the most extensively validated in hospital based and population based settings as well as a wide range of ethnic groups (box 2).[5 w9] Many healthcare professionals will not need diagnostic criteria in routine clinical practice, however, although such criteria may help diagnose borderline cases.[6]

SUMMARY POINTS

- Eczema is associated with serious morbidity for the patient and family
- Patient education is essential for the treatment of this complex chronic disorder
- Topical anti-inflammatory drugs together with regular use of emollients is effective in most children with eczema
- Patients with eczema are susceptible to molluscum contagiosum and infection with *Staphylococcus aureus* and herpes simplex virus; infections can cause disease flares and treatment resistance
- Patients with severe eczema may need systemic immunomodulatory drugs, which require close monitoring by a doctor experienced in their use

SOURCES AND SELECTION CRITERIA

We searched Medline, the Cochrane Collaboration, and the GREAT database (www.greatdatabase.co.uk) using the search terms "eczema", "atopic eczema", "atopic dermatitis", "management", and "treatment". When possible, evidence from randomised controlled trials and systemic reviews was used. Case series were used in the absence of higher level evidence. We also referenced expert review articles and included expert opinion based on clinical experience.

Box 1 | Clinical features of eczema

Clinical manifestations vary with age:

- Typically starts in early infancy with eczematous, erythematous papules and vesicles on the cheeks and scalp; scratching causes crusted erosions (often non-flexural areas)
- After infancy it is often limited to the flexures but may also affect the nape of the neck and extensor surfaces of the limbs; moderate to severe eczema can be much more extensive
- Infections with *Staphylococcus aureus* are common and cause typical honey yellow crusts

Eczema presents differently in Asian, African, and Afro-Carribean children:

- Skin can appear darkened rather than erythematous
- Extensive lichenification and prurigo lesions can occur
- Follicular and discoid patterns of atopic eczema are more common in children with darker skin

Box 2 | UK refinement of the Hanifin and Rajka diagnostic criteria[5]

To qualify as having atopic dermatitis/eczema, the child must have had an itchy skin condition in the past 12 months plus three or more of the following criteria:

- Onset below age 2 years*
- History of flexural involvement
- History of a generally dry skin
- Personal history of other atopic disease**
- Visible flexural dermatitis

*Not used in children under 4 years.

**In children under 4 years, a history of atopic disease in a first degree relative may be included.

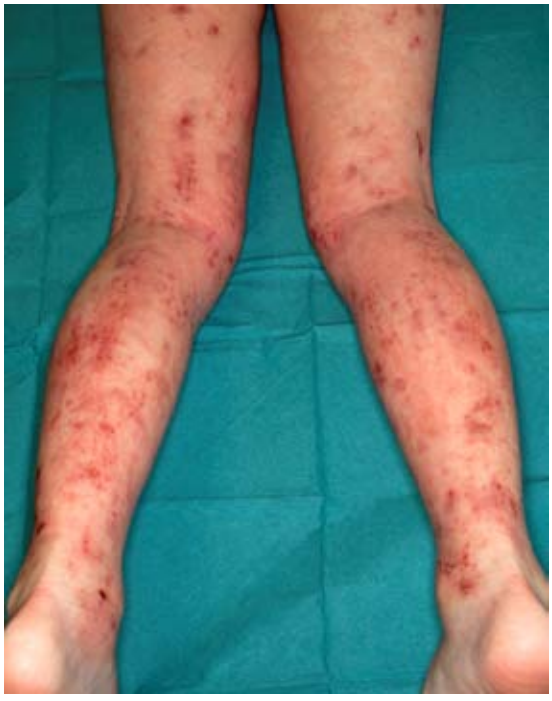

Fig 1 | This child had severe eczema despite maximal topical treatment and inpatient management

Approach to management

Severe eczema is a physically and psychologically demanding disease and requires a comprehensive, holistic, medium term or long term strategy (fig 1). Treatment aims to reduce the symptoms, improve quality of life, and decrease the degree and frequency of flares. Furthermore, treatment may modify the overall disease course and possibly reduce atopic comorbidities,[7] although more evidence is needed to determine if this is a robust effect. A personalised management plan is essential to ensure adherence to treatment recommendations and treatment success. The management of severe eczema in children often requires a multidisciplinary team approach.

Managing eczema in primary care

Mild eczema can be managed in primary care with patient education, regular use of emollients, and topical corticosteroids of mild or moderate potency. The National Institute for Health and Clinical Excellence (NICE) has published guidelines on the treatment of eczema in children.[8]

Patient education

Patient education is an essential and important primary intervention. It has been shown to reduce disease severity and improve quality of life at least over a one year period.[9 10] A randomised controlled trial (RCT) concluded that nurses may be better placed to offer educational support, but intervention studies are needed to confirm this.[w10]

Bathing and emollients

Daily use of emollients to counteract dry skin is one of the cornerstones of management. Bathing hydrates and cleanses the skin and emollient based soap substitutes moisturise the skin and avoid skin irritation associated with standard soaps. Bathing is usually recommended once a day and emollients once to twice a day, or even more often, depending on the clinical setting.[11] Ointments contain higher concentrations of lipids and are generally more effective moisturisers than creams. Topical preparations should be free of dyes, fragrances, and food derived allergens such as peanut protein.[7] Despite the universal recommendation of the use of emollients and bath additives, no robust evidence from RCTs supports this.[12 13] Of note, the 2007 NICE guidelines recommended that aqueous cream should not be used because it can cause irritant reactions.[8] More recently, aqueous cream was shown to increase transepidermal water loss in healthy subjects and those with a history of eczema.[w11 w12] Despite this, aqueous cream is still the most commonly prescribed emollient in England.[w12]

Topical corticosteroids

Topical corticosteroids are widely used as first and second line agents in the management of eczema. These drugs have anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive actions. Topical corticosteroids are grouped by potency (box 3), and prescribers should tailor them to the severity of the eczema. A proactive rather than reactive approach to treatment is favoured—long term moisturising treatment to maintain remission with short term "step-up" treatment for flares.[11] Corticosteroids of

mild to moderate potency are used for maintenance treatment in mild to moderate eczema. Flares are managed with short courses (7-14 days) of such preparations. Do not use long term potent corticosteroids in children without specialist advice. Itch is a key symptom for evaluating response to treatment.[11]

Local adverse effects, such as skin atrophy, striae, and telangiectasia, can occur with inappropriate use of topical corticosteroids, especially on sensitive areas such as the face, neck, or groin. Systemic adverse effects are rare.[7] A systematic review of 10 RCTs found no evidence that application of topical corticosteroids twice daily is more efficacious than once daily application. Furthermore, once daily application may increase adherence to treatment and reduce side effects and costs.[13 14] When eczema is not controlled despite potent topical corticosteroids and full adherence to the prescribed emollient and bathing regimen, or when unsafe amounts of potent topical corticosteroids are needed, additional therapeutic approaches are required.

Antimicrobial treatments

Eczema flares are often attributable to infection, most commonly with *Staphylococcus aureus*. These infections can be clinically subtle.[4] Signs of bacterial infection include weeping, crusts, pustules, failure to respond to treatment, and rapidly worsening eczema. However, although skin infection undoubtedly plays a role in eczema flares, two Cochrane reviews of anti-staphylococcal measures (prophylactic and treatment) in routine eczema care found no clear evidence of additional clinical benefit.[15 16] Nevertheless, it is still accepted clinical practice to use antimicrobial measures in patients with frequent skin infections. Combined corticosteroid and antimicrobial ointments can be used for short periods in infected eczema, but a course of oral antibiotics may be equally effective and bacterial resistance may be less likely to develop. An investigator blinded RCT of 31 patients (aged 6 months to 17 years) with moderate to severe clinically infected eczema reported that bleach baths (0.005% sodium hypochlorite), used together with intermittent nasal mupirocin, decreased the severity of eczema over three months.[17] However, the results could be explained by regression to the mean, and more evidence is needed to determine the exact role of such antiseptic measures in routine clinical practice.

Children with severe eczema are also at increased risk of eczema herpeticum (fig 2), which can be recurrent.[18]

Box 3 | Topical corticosteroid potency classes

Mild: 1% hydrocortisone

Moderate: Betamethasone valerate 0.025% (Betnovate-RD) and clobetasone butyrate 0.05% (Eumovate)

Potent: Betamethasone valerate 0.1% (Betnovate), hydrocortisone butyrate 0.1% (Locoid), mometasone furoate 0.1% (Elocon)

Suprapotent: Clobetasol propionate 0.05% (Dermovate)

Combined antimicrobials and corticosteroid: Hydrocortisone acetate 1% (mild) + fusidic acid 2% (Fucidin H); clobetasone butyrate 0.05% (moderate) + oxytetracycline 3% + nystatin (Trimovate); betamethosone valerate 0.1% (potent) + fusidic acid 2% (Fucibet); hydrocortisone butyrate 0.1% (potent) + chlorquinadol 3% (Locoid C)

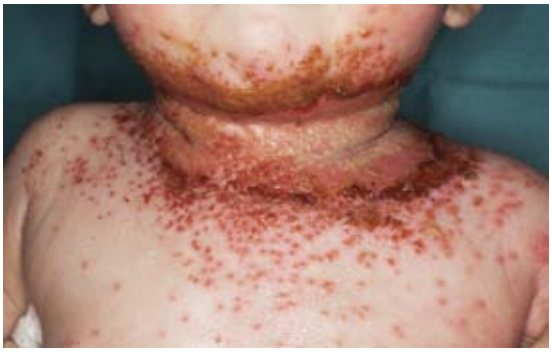

Fig 2 | This baby had eczema herpeticum. After an incubation period of 5-12 days, eczema herpeticum presents as multiple, disseminated, vesiculopustular lesions and painful punched out erosions

Early diagnosis and prompt treatment are essential, and parents should be educated about the clinical signs and the need to seek medical advice. Chickenpox and viral warts can be more severe in children with eczema. Molluscum contagiosum is common in children with eczema and can flare the disease when infected.

Colonisation with the yeast *Malassezia furfur* can also complicate eczema, particularly in the head and neck areas. Clues are a sharp cut-off line between affected and unaffected skin and only partial response to topical anti-inflammatory drugs. In such cases, the addition of a topical antifungal agent can result in great improvement.[w13]

Antihistamines

Systemic antihistamines are widely prescribed in eczema in the belief that they will reduce itch. The role of histamine in the itch of eczema is unclear, and it may play only a small part.[11] There is no good quality evidence for the usefulness of antihistamines in the management of eczema, and they are not routinely recommended. In an acute flare of eczema with serious sleep disturbance, children over 6 months of age can be offered a trial of an appropriate sedating antihistamine.[8]

When should a child with eczema be referred for specialist care?

Comprehensive referral advice is detailed in the recent NICE guidelines.[8] Referral to secondary care is recommended for several clinical scenarios, including if the diagnosis is uncertain, if the disease is not controlled satisfactorily with appropriate first line treatments, if there are severe or recurrent skin infections, if facial eczema is uncontrolled, if there are serious psychological problems, if the carers need specialist advice on treatment application, or if the child or parent(s) has serious disease associated social or psychological problems. In addition, children with moderate or severe food allergy or growth delay should be referred.[8]

What is severe eczema?

No universally agreed definition of severe eczema exists, but from a clinical point of view, severe disease is eczema that is resistant to first line topical treatments and has a considerable impact on quality of life. The European Taskforce on Atopic Dermatitis defined severe atopic dermatitis

Box 4 | Approach to non-response to first line treatment

Assess adherence to treatment recommendations and technique—look at how much of the topical agent is being applied and directly observe application

Look for the presence of *Staphylococcus aureus* and herpes simplex infection

Consider whether allergens might be exacerbating the disease—immediate-type allergy to foods and aeroallergens as well as delayed-type hypersensitivity to a contact allergen, including topically applied drugs

Box 5 | Potential triggers for eczema

Irritants: Hard soaps, detergents, fragrances

Infections: Molluscum contagiosum or infection with *Staphyloccocus aureus*, herpes simplex

Overheating

Psychological stress

Aeroallergens: Pollens, grasses, animal dander, house dust mites

Food allergens: In particular, egg, peanut, and cow's milk

as having an eczema severity score (SCORAD) greater than 40 or "persistent" disease, whereas the NICE eczema guidelines refer to "widespread areas of dry skin, incessant itching, and skin redness," but there is no universal consensus on what constitutes a severe case or persistent disease.[11]

The use of validated and reliable severity scores in eczema is important in documenting the treatment response to systemic treatments. It is particularly important to balance safety concerns with efficacious treatment in children, and objective outcome scores can facilitate this. Of 20 severity scales, only three—the scoring atopic dermatitis index (SCORAD), the eczema area and severity index (EASI), and the patient oriented eczema measure (POEM) scores—have been adequately tested.[3 6] The infant's dermatitis quality of life index (IDQOL) and children's dermatology life quality index (CDLQI) are useful and validated quality of life metrics in children with skin disease.[1]

How common is severe childhood eczema?

Most cases of childhood eczema are mild, but severe eczema is a challenge to manage. A UK study of 1760 children with eczema found that 84% had mild disease, 14% were classified as moderate, and 2% had severe disease.[w14] A Norwegian population survey reported similar findings.[w15]

How is severe eczema managed?

Topical calcineurin inhibitors

Topical calcineurin inhibitors (tacrolimus ointment 0.03% or 0.1% and pimecrolimus ointment 1%) block the production and release of proinflammatory cytokines.[7] They are approved by the Food and Drug Administration and European Medicines Agency as second line agents for the short term and pulsed long term treatment of moderate to severe eczema in immunocompetent patients aged over 2 years. NICE guidelines for childhood eczema recommend their use when first line treatment of moderate to severe eczema with potent topical corticosteroids is contraindicated or has failed in children aged 2 years or more. They are also beneficial in areas of delicate skin, such as around the eyes, the face, the neck, and the nappy area, where the use of potent corticosteroids can cause skin atrophy. NICE recommends that calcineurin inhibitors are used only by physicians (including general practitioners) with a special interest and experience in dermatology.

A systematic review and meta-analysis showed that twice weekly application of either 0.1% tacrolimus ointment or a potent topical corticosteroid (weekend therapy) in patients with stable eczema, compared with vehicle (excipient) alone, significantly increased the time between disease exacerbations and increased the total number of disease-free days.[19] The safety profiles of calcineurin inhibitors are overall reassuring to date, and no causal link with cancer has been shown.[12 20] However, early but unconfirmed epidemiological evidence has emerged of an increased risk of cutaneous lymphoma, but longer term data are needed.[w16]

Occlusive treatments (wet wraps)

Occlusion of the skin is widely used in severe eczema. Occlusive dressings increase skin hydration, act as a barrier to scratching, and promote restful sleep. The occlusion also promotes penetration of topical corticosteroids. However, wet wraps can exacerbate infections and increase dryness if not used appropriately, and patients and parents need to be educated in their use.[7] The wraps consist of a bottom (wet) and top (dry) layer. They are generally left in place overnight and applied for five to seven days in a row. In a critical review of 11 studies, only two of which were RCTs, wet wraps were reported as a useful short term treatment to induce disease remission.[20]

Box 6 | Pretreatment screening and other considerations for systemic immunosuppressant treatment in eczema

Pretreatment screening for infections includes testing for viral hepatitis, tuberculosis, and HIV, in addition to varicella zoster virus antibody (immune status), depending on the population being treated

Pregnancy prevention should be considered when appropriate. Food and Drug Administration pregnancy categories are: ciclosporin: C, azathioprine: D, mycophenolate mofetil: D, and methotrexate: X

Live vaccines (such as measles, mumps, and rubella; yellow fever; typhoid) are contraindicated while taking ciclosporin, methotrexate, and azathioprine

Killed vaccines (such as influenza, hepatitis A, polio, rabies) are less likely to induce immunity in immunosuppressed patients

Immunosuppressed patients may have more severe forms of infections such as influenza, and vaccination is therefore advised in patients taking systemic immunosuppressants; annual pneumococcal and influenza vaccination is recommended

Patients and parents should be told about avoiding direct sun while on immunosuppressants because of the increased risk of skin cancer

Check vitamin D values before and during treatment and supplement as needed (Sun avoidance is recommended in immunosuppressed patients, and this will increase the likelihood of vitamin D deficiency, which is common in northern regions.)

Each treatment has individual screening protocols for renal, hepatic, and bone marrow impairment, and prescribers need to be familiar with these

A full and frank discussion with children and parents about the risk-benefit balance is needed before treatment is started

A PATIENT'S PERSPECTIVE (A, AGED 8 YEARS)

When I had eczema it was hard for me not to scratch. I hated getting blood on my clothes. I felt sad not being able to do stuff like everybody else—not being able to swim and not being able to walk properly. I hated people saying things about my skin and getting in trouble for scratching. When I thought about my skin, scary questions came into my head. Would the eczema go away? Would I ever look normal? Would people laugh at me?

After treatment I feel so much happier. I can do stuff like everybody else. Life is so much easier now. Now my skin is better I don't have to worry about people laughing at me. I don't have to wear gloves at night to stop me scratching. Now I feel just like everybody else.

The mother's story

One of the hardest things was the sleep deprivation. One night seemed to roll into another. As parents we felt out of our depth. Our other children felt neglected as all of our time was consumed by A's skin and creams, baths, and bandages, as well as washing clothes and sheets because they were soiled with blood. It was stressful watching her scratch herself to pieces and nothing we did or said could stop her. The condition can get out of control, not only medically but in the way it affects your mind. It was the worst thing we have been through as a family. I feel blessed to have come out the other side. It may not be a terminal illness but it was very hard to cope with. We now feel we have control of her condition with the help of her medications. We have learnt so much along the way and now just look ahead to good times.

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

Centre of Evidence Based Dermatology (www.nottingham.ac.uk/scs/divisions/evidencebaseddermatology/index.aspx)—Evidence based dermatology website including information from the Cochrane Skin Group, the UK Clinical Trials Dermatology Network, and the NHS Evidence website

Cochrane Skin Group (http://skin.cochrane.org)—Evidence based dermatology website with systematic reviews

Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic dermatitis. *Health Technol Assess* 2000;4:37. www.hta.ac.uk/fullmono/mon437.pdf

National Institute for Health and Clinical Excellence. Atopic eczema in children. CG57. 2007. http://guidance.nice.org.uk/CG57

Information resources for patients

National Eczema Association (www.eczema.org)—UK website with information for parents on eczema and general management principles

National Eczema Association (www.nationaleczema.org)—US website on eczema for patients and parents, which includes information for schools and teachers

Under My Skin (www.undermyskin.com)—Online books for children with eczema

DermNet NZ (www.dermnetnz.org/dermatitis/treatment.html)—Information for patients and parents on treatments for eczema

Ultraviolet light treatment

A systematic review of nine RCTs of ultraviolet light treatment found it to be effective compared with placebo.[21] It can help to delay or prevent the need for systemic immunomodulatory drugs, especially in children with dark (type V and VI) skin. The inability to comply with safe treatment may, however, preclude its use in younger children, and the practical aspect of treatment three times a week for several months may be difficult for some families. In addition, the long term risk of skin cancer is unknown and of particular concern in white children. When considering such treatment for severe eczema, the doctor should also be aware of the possible need for systemic immunomodulatory drugs later on because such treatment would further increase the risk of skin cancer.

Systemic immunomodulatory treatments

Children with severe eczema may require systemic immunosuppression to achieve disease control. Before considering such therapies, explore the possible reasons for the failure of first and second line treatments (boxes 4 and 5). Topical treatments require some expertise and can be labour intensive for families. Patients with disease refractory to standard treatments can be admitted to hospital or day care for observation of treatment application and response, before treatment is deemed a failure.

Systemic immunomodulatory drugs in severe eczema are not licensed for use in children and adolescents, apart from ciclosporin A, which is licensed in Germany for the management of eczema in patients over 16 years of age. The evidence base for usage and safety of these drugs in childhood eczema is not well established; practice has to be guided by experience in adult patients and the use of these drugs in other severe childhood inflammatory disorders, neither of which is ideal. Differences in prescribing across geographical regions are largely the result of established custom and practice and the familiarity of individual prescribers with the different agents, rather than being based on best evidence, and this is an area that urgently requires more intervention studies. All immunomodulatory drugs need pretreatment screening investigations, as well as close monitoring for side effects throughout the duration of treatment (box 6).

Ciclosporin A

Ciclosporin is a potent inhibitor of T cell dependent immune responses and interleukin 2 production. It is fast acting, allowing prompt induction of remission in severe eczema. The most notable side effects of nephrotoxicity and hypertension limit long term treatment. Ciclosporin A is therefore used as a short term treatment or as a bridge between treatments.

A systematic review of 10 RCTs investigating ciclosporin found that it is more effective in eczema than placebo but that relapse is rapid once treatment is stopped, with clinical scores often returning to baseline values within eight weeks.[13] A systematic review of 11 prospective clinical studies of ciclosporin A found that all showed decreased disease activity.[22] The effectiveness of ciclosporin A was similar in children and adults,[22] with younger patients showing greater tolerance.[23]

Azathioprine

Azathioprine is an inhibitor of purine synthesis that reduces the proliferation of leucocytes. The target cells and mechanism of action in eczema are not fully elucidated.[24] Azathioprine has a complex metabolism with several immunosupressant metabolites. The balance between

TIPS FOR NON-SPECIALISTS

Explore the effect of the condition on the child's sleep, schooling, sports, social activities, and family life. Acknowledging and, if possible, dealing with these stressors can improve management

Ensure that topical treatments, including emollients and topical corticosteroids, are being applied correctly. Education of patients and parents is vital. Directly observed treatment is useful in determining the adherence of patients and parents to treatment

Phobia about using topical corticosteroids is a common cause of non-adherence and needs to be dealt with

Consider skin infection, which can be clinically subtle, in patients who do not respond to first line treatment

Patients on systemic drugs need frequent expert assessments for treatment response, changes in disease status, and potential side effects

QUESTIONS AND AREAS FOR FUTURE RESEARCH

Does the regular use of emollients directly after birth in high risk children reduce the risk of developing eczema?

How effective are nurse led educational interventions?

Does treating eczema early prevent severe disease?

Does early intervention prevent respiratory allergies in later life?

Do robust eczema endophenotypes exist? If so, could personalised treatment be developed?

Which are the safest and most effective systemic immunosuppressive strategies for severe disease?

A recent priority setting exercise by the James Lind Alliance involving patients and professionals identified 14 priority areas[w23]

thiopurine metabolites is governed by thiopurine methyltransferase (TPMT) activity.[24] The pre-treatment determination of *TPMT* genotype or activity level allows informed drug dosing to minimise myelotoxicity. Other side effects include headache and gastrointestinal upset, hepatotoxicity, and drug hypersensitivity. Azathioprine has a slow onset of action, with a notable clinical improvement at two to eight weeks into treatment.[w17] A double blind placebo controlled crossover RCT of eczema in adults reported that azathioprine significantly improved quality of life measures. There was a mean reduction in disease activity of 27% after 12 weeks of treatment.[25] In a series of 28 children with severe eczema treated with azathioprine, 17 reported significant improvement, six some improvement, and five no improvement. Laboratory abnormalities were seen in seven patients and the dose had to be adjusted.[26] Personal experience is that patients treated with azathioprine take longer to respond and do not rebound as often or as rapidly as those treated with ciclosporin when treatment is stopped.

Methotrexate

Methotrexate is commonly used for other chronic inflammatory diseases including adult psoriasis and childhood arthritis. Its mode of action is not fully understood, but it has anti-inflammatory effects and reduces allergen specific T cell activity.[w18] It is thought to augment concentrations of adenosine, which acts as an endogenous anti-inflammatory agent by mediating cytokine release and adhesion molecule expression, as well as by binding to adenosine cell surface receptors.[27] Gastrointestinal disturbance, liver function abnormalities, and bone marrow suppression are potential side effects, although the drug is generally well tolerated.[27] Evidence for the use of methotrexate in eczema is limited, with a single RCT of methotrexate use in adults.[28] This was a single blind parallel group RCT in 42 patients with severe eczema. Patients were randomly assigned to receive methotrexate or azathioprine for 12 weeks. This study suggests that methotrexate and azathioprine are equally effective in treating eczema in the short term, but larger adequately powered studies with longer follow-up are needed.[w19] A case series of 25 children with refractory discoid eczema treated with methotrexate reported that eczema had cleared in 16 and almost cleared in three. The drug was well tolerated and no adverse events were seen.[29]

Mycophenolate mofetil

Mycophenolate mofetil selectively and reversibly inhibits inosine monophosphate dehydrogenase, which suppresses the de novo pathway of purine synthesis, resulting in selective suppression of lymphocyte function. Unwanted effects on other cell types are minimised. The most common side effect is gastrointestinal disturbance. Mild increases in serum concentrations of liver enzymes are also reported. Severe bone marrow suppression is uncommon.[30] This drug is used in recalcitrant eczema, although no controlled studies have investigated its efficacy. A retrospective case series of 14 children with severe eczema treated with mycophenolate mofetil reported that eczema cleared completely in four and that four children had an excellent response, five a good response, and one an inadequate response. The drug was well tolerated in all patients.[30] In a case series of 12 children who moved from azathioprine to mycophenolate for management of their eczema, eight were reported to have significant improvement and four no improvement.[26]

Are there any new treatment targets for severe eczema?

It is hoped that new insights into the complex pathophysiology of eczema will allow more targeted treatments aimed at dysregulated structural or immune functions, and that a better understanding of eczema endophenotypes will facilitate a more individualised approach to treatment. Furthermore, insights into filaggrin synthesis and function will facilitate strategies aimed at increasing its expression.[w20] Agents that induce antimicrobial peptides might reduce the risk of skin infection,[w20] and biological agents that influence the early development of specific B cell and T cell clones may help reduce the inflammatory cascade.[w21] All this requires more basic research and, eventually, well designed RCTs with clearly defined diagnostic criteria and outcome domains related to disease severity, long term control of flares, and patients' quality of life.[w22]

Thanks to Rosemarie Watson for providing figure 2.

Contributors: MMcA and AI planned the article; MMcA did the background reading, prepared the first draft, and amended subsequent drafts after input from CF and ADI. ADI is guarantor.

Funding: None received.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Not commissioned; externally peer reviewed.

Patient and parental consent obtained.

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Accepted: 2 July 2012

ANSWERS TO ENDGAMES, p 46

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CASE REPORT A human bite

1 The most immediate concern is the presence of a life threatening injury or fracture sustained through the head trauma. Human (and animal) bite wounds are also particularly susceptible to infection because of the multiple organisms found in saliva.
2 A seven day course of co-amoxiclav.
3 Consider tetanus prophylaxis in all patients who present with human or animal bites.
4 The patient is also at risk of HIV and hepatitis B, and the appropriate post-exposure prophylaxis should be discussed with an infectious diseases specialist.
5 Once any life threatening injuries have been excluded, a comprehensive history—including tetanus status and a thorough examination of the wound and surrounding structures—should be undertaken, noting the presence of any infection.
5 Encourage the wound to bleed and irrigate with warm running water or normal saline. Analgesia (paracetamol or ibuprofen) should be given if needed, in addition to prophylactic antibiotics and tetanus prophylaxis.
5 The exposed ear cartilage should be dressed and the patient referred to the plastic surgery unit for further debridement and appropriate reconstructive surgery.

STATISTICAL QUESTION
Confidence intervals and statistical significance: rules of thumb

Statements *a* and *c* can be concluded, whereas *b* cannot.

ANATOMY QUIZ
Coronal section of brain

A: Sagittal sinus
B: Interhemispheric fissure
C: Left lateral horn
D: Left temporal lobe
E: Lateral sulcus or sylvian fissure