

EVIDENCE BASED MANAGEMENT OF ATOPIC ECZEMA

BEST PRACTICE

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Atopic eczema (AE, synonymous with atopic dermatitis), together with asthma and hay fever, has been on the increase for at least three decades. At present, around 15–20% of children in industrialised countries suffer from AE, leading to a significant reduction in quality of life and a burden on health care resources.^{1,2} Paediatricians encounter patients with AE both “on call” and in outpatient clinics and are therefore often directly involved in AE management and patient education. Paediatricians who run asthma clinics encounter AE frequently. In addition, a few paediatricians have a special interest in AE, and some even run dedicated paediatric dermatology outpatient clinics. This review focuses on the practical management of AE from a paediatric perspective, with an emphasis on relating treatment decisions to the currently available evidence. Sufficient evidence from clinical trials is now available to inform many areas of AE management, although some “grey areas” and some areas of relative ignorance remain. We will illustrate common AE management issues in case scenarios and use these to discuss the place of emollients, topical steroids, the new topical immunomodulators (tacrolimus and pimecrolimus), “wet wrap” bandages, as well as systemic treatment options, phototherapy, and advice on allergen avoidance and complementary therapies.

Much of the evidence in this article is based on a Health Technology Assessment report that was commissioned by the National Health Service in 2000, supplemented by other studies that have been published since.³ We also refer to our practical experience in running a multi-professional eczema clinic at the Queen’s Medical Centre, Nottingham.

EMOLLIENTS AND TOPICAL CORTICOSTEROIDS

Case history A

Marc, age 2 years, attends your asthma clinic. On his third visit, Marc’s father tells you that he has developed an itchy widespread rash (fig 1). Examination reveals widespread, ill defined erythematous patches, with more pronounced involvement in the skin folds. You are satisfied that he fulfils the UK diagnostic criteria for AE⁴ (table 1). Marc is currently using both a moisturiser and 1% hydrocortisone ointment twice a day.

Emollient treatment probably has an important role in AE management, although its use is supported by relatively few good studies.⁵ Emollients can often be sufficient to provide relief in children with very mild eczema, especially when using greasier preparations such as white soft paraffin/liquid paraffin in a 50:50 mixture. The best emollient is the one that the child will actually use, and a tray of different emollients set up in the clinic area can be a good way to empower the older child to select his/her own emollient. If applied two or three times daily to the whole body, an 8 year old child will require at least 250 g per week. Emollients alone are not so useful during acute inflammatory flares when additional topical steroids will be needed. The basic principle is to use the least potent steroid required to control the AE on a daily basis, until the skin has cleared. Current evidence suggests that short bursts of a potent topical steroid (once or twice daily), followed by “holiday periods” of just emollient use, are as effective and safe as long term treatment with low dose topical steroid.³ Steroid dilutions and topical steroid–antibiotic combinations should be avoided, as there is little evidence that they have superior treatment efficacy in comparison to topical steroids alone. Bacterial resistance development may be a problem in antibiotic containing preparations.

A recent National Institute for Clinical Excellence (NICE) appraisal evaluated the clinical trial evidence for different frequencies of application for topical corticosteroids and commented, “Overall, studies found little difference in response to treatment between once-daily and twice-daily application of potent topical corticosteroids” and that “Some statistically significant differences favouring twice-daily treatment were identified, but these were inconsistent between outcome assessors (physicians versus patients) and outcomes selected for analysis”.⁶ We now routinely use all our topical steroids once daily. This has simplified treatment plans for busy

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Figure 1 Widespread, poorly demarcated redness with associated surface dryness typical of atopic eczema in a young child.

parents, halved the costs of treatment for health care commissioners, and possibly reduced adverse events such as skin thinning without any noticeable loss of efficacy.

One practical point with regards to the concomitant use of topical steroids and emollients is to discourage the application of one immediately after the other. Such simultaneous use may dilute or inactivate the therapeutic effect of the topical steroid and possibly spread the topical steroid to non-affected areas of skin. While emollients can be applied during the same day as topical steroids, their application should be done at separate times to avoid such possible dilution and contamination effects. Although we could not find any evidence of exactly how long a gap should be left between the application of a topical corticosteroid and subsequent application of an emollient, we recommend at least one hour to parents attending our clinic.

PATIENT EDUCATION: ROLE OF PAEDIATRIC OR DERMATOLOGY NURSE

One of the most important aspects of AE management is patient education, including advice on what topical treatments to use, and when and how to use them.⁷ This *requires time* that is often not available in a busy paediatric outpatient or ward setting. Nurses with a special interest and additional training in dermatology can offer patient education in an outpatient setting or during home visits in the community.^{7, 8} They can demonstrate to patients how to apply the treatment and can provide a personalised written management plan in agreement with the family and team physician. A recent study has shown that patient education from a nurse practitioner may be able to improve patient concordance and, as a consequence, can reduce the unnecessary use of topical steroids in AE.⁹

ROLE OF TOPICAL IMMUNOMODULATORS AND BANDAGE THERAPY

Case history A (continued)

You prescribe one week of 0.1% betamethasone valerate ointment, followed by a “holiday period” of moisturiser only. You have asked his parents to use three-day bursts of 0.1% betamethasone valerate for future, milder flares. Marc sees you again two months later, mainly for his asthma. According to Marc’s mother, his “eczema is no better, Doctor”. In fact, on

Table 1 UK diagnostic criteria for atopic dermatitis⁴

Presence of an itchy skin condition over the past 12 months

Plus three or more of the following:

- ▶ Onset below the age of 2 years
- ▶ History of flexural involvement (around the eyes, around the neck, front of elbows, behind the knees, front of ankles)
- ▶ Generally dry skin
- ▶ Personal or (in children under four years) family history of atopic disease
- ▶ Visible flexural dermatitis (around the eyes, around the neck, front of elbows, behind the knees, front of ankles)

examination you find Marc’s skin is worse than ever. As it turns out, none of the 0.1% betamethasone valerate has reached Marc’s skin because of his mother’s concerns about “steroids” causing skin thinning.

Parental fears about the use of topical steroid are very common and will affect patient concordance.¹⁰ It is important to explain to Marc’s mother that there is currently little evidence to suggest that topical steroids will cause skin thinning or significant adrenal axis suppression, provided they are used in short bursts.^{11, 12} However, if Marc’s parents are not keen to use topical steroids despite your advice, two other options might be considered for moderate to severe eczema: topical tacrolimus and “wet wraps” or ichthopaste bandages. Both forms of treatment are discussed below.

Tacrolimus and pimecrolimus

Tacrolimus was initially developed as an immunosuppressive agent to prevent organ transplant rejection, and has been formulated into an ointment available as 0.1% and 0.03% strengths. Tacrolimus 0.1% ointment is probably as strong as betamethasone valerate (a potent topical steroid), and it is currently recommended by the manufacturer for patients with moderate to severe AE who have failed to respond adequately to conventional treatment.¹³ NICE has recently reviewed the clinical trial evidence for prescribing topical tacrolimus in detail and has concluded that it can be used by physicians with a special interest in AE “for the second-line treatment of moderate to severe atopic eczema that has not been controlled by adequate use of appropriate potency topical corticosteroids and where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy”.¹⁴ Tacrolimus might prove to be particularly useful in delicate areas such as the face and neck areas, where the skin thinning effects of moderate to potent topical steroids might be more of a problem because of the sensitivity of such sites to skin thinning.¹⁵

Pimecrolimus is another topical immunosuppressive agent, more potent than vehicle alone but less potent than 0.1% betamethasone valerate or tacrolimus.¹⁶ Unlike tacrolimus, licensed use of pimecrolimus in the UK is not restricted to patients who are unresponsive to, or intolerant of, conventional treatment. Its role in the treatment of AE is currently uncertain because of the lack of comparative data to standard treatment for mild AE—that is, 1% hydrocortisone ointment. There is, however, some evidence that pimecrolimus is effective in preventing flares of AE in comparison to vehicle.¹⁶ The NICE consultation document has stated that pimecrolimus may also be used as a second

Tacrolimus: some facts

- ▶ Used twice a day initially
- ▶ Only licensed in children above 2 years
- ▶ Children aged 2–15 years are only allowed 0.03% tacrolimus
- ▶ A burning sensation is common after application but this settles after a few days
- ▶ Should not be applied to infected eczematous skin
- ▶ Particularly useful for persistent severe facial eczema
- ▶ Use of tacrolimus is recommended up to one week after full AE clearance.
- ▶ Systemic absorption is minimal, but long term data are needed to alleviate concerns about reports of skin cancer in animal studies.
- ▶ The safety of tacrolimus under occlusion has not been evaluated
- ▶ Tacrolimus is at least 10 times more expensive than topical steroids

line agent for unresponsive head and neck eczema.¹⁴ Long term safety studies are lacking for both tacrolimus and pimecrolimus.

“Wet wraps” bandages

“Wet wraps” are occasionally a helpful tool in the treatment of moderate to severe AE, especially in infants and young children where limb scratching is a major problem. “Wet wrapping” involves the application of a weak topical corticosteroid (for example, 1% hydrocortisone ointment) or just emollient under an inner wet and an outer dry layer of cotton tubular bandages or garment.¹⁷ However, at present clear clinical evidence for the effectiveness of “wet wraps” is very limited.^{18–20} The same is true for the use of impregnated bandages such as ichthopaste, sometimes used in older children. From our clinical experience, the latter can be particularly helpful to reduce thickened areas of AE on the child’s limbs where habitual scratching has led to the development of an intractable itch-scratch-itch cycle.

With regard to the safety of wet wrap bandages, some doctors are concerned about the potential risk of hypothalamic–pituitary–adrenal (HPA) axis suppression with the use of topical steroids, especially if applied under occlusion.²¹ Only very few studies have addressed this issue. These suggest that wet wrap dressing with topical steroid does not significantly affect short term growth or the HPA axis.²² However, large, well designed, long term studies are currently missing.

DIETARY ADVICE, TYPE OF CLOTHING, WASHING POWDER, HOUSE DUST MITE ERADICATION, AND COMPLEMENTARY THERAPIES**Case history A (continued)**

You prescribe “wet wraps” with emollients only applied underneath the bandages, and your paediatric community nurse with a special interest in AE teaches Marc’s parents how to apply the bandages. Following this, Marc does well. When you see him a few months later, his mother comes to you with a few more questions. She wonders if keeping Marc off cow’s milk and egg products could help his AE. She would also consider buying a special mattress and pillow covers for Marc’s bed if you recommend it, and asks if you would like to perform “allergy testing to see what

causes his eczema”. Finally, she asks you about your view on complementary therapies in AE.

A clear history of AE exacerbation after ingestion of a certain food warrants a trial of dietary manipulation under the guidance of a paediatric dietician.²³ In general, infants tend to benefit most from such dietary measures—for example, a six week supervised trial on hydrolysate infant formula, excluding egg and cow’s milk.²³

Many people recommend non-biological washing powder. However, there is currently no evidence to suggest that non-biological washing powder is any better than their biological counterparts.²³

Cotton clothing seems to have a soothing effect, but this is most likely because of the smooth textile fibres of cotton.²³ Furthermore, rigorous house dust mite eradication methods have been shown to reduce disease severity under experimental conditions. However, they are very time consuming and costly and no more effective than simple bed covers.²³

In case of suspected concomitant food allergy a referral to a paediatric allergy clinic should be considered.²⁴ Children with persistent hand or foot eczema may benefit from patch testing, as occasionally such a pattern of eczema could be caused by a superimposed allergic contact dermatitis from substances such as lanolin (found in creams) or rubber (found in shoes).

With regard to complementary therapies, there is limited evidence that systemic traditional Chinese medicine compared with placebo can improve AE in children.²⁵ Clinical trials on other complementary therapies, such as homoeopathic remedies, acupuncture, hypnotherapy, and aromatherapy has as yet not shown any clear benefit.³

INFECTIVE EXACERBATIONS OF ATOPIC ECZEMA**Case history B**

The following week, Marc’s baby brother, Peter, who has also developed AE, is sent to you as an urgent referral because of rapidly deteriorating eczema. His father thinks he has a temperature. On examination, Peter has widespread, very inflamed and oozing acute eczema (fig 2).

Herpes simplex infection is a possibility, although bacterial infection is more likely given the presentation with weeping, crusting, and pustule formation. Eczema herpeticum usually



Figure 2 Intense red and oozing infected atopic eczema in an infant.



Figure 3 Discrete, punched-out erosions and crusts in an older child with eczema herpeticum.

shows multiple discrete vesicles and erosions (fig 3). A skin swab for virology and bacteriology should be taken and acute hospital referral be considered.

In a child with AE secondarily infected by bacteria, topical steroid cream can be continued in areas that are not too moist, and oral flucloxacillin (or erythromycin if penicillin allergic) should be given for a week for suspected bacterial infection, since *Staphylococcus aureus* is by far the most common infective organism.²⁶ Eczema herpeticum is treated with systemic aciclovir. After the infection has settled, it is worth exploring the reasons for the exacerbation further, such as under-treatment with topical corticosteroids or simply running out of adequate supplies.

DISCOID ECZEMA

Case B (continued)

Peter makes a dramatic recovery, but he is re-referred to your clinic two months later with a “new” skin rash that his doctor thought was a fungal infection (fig 4). Peter’s mother tells you that Peter rubs the new rash “like crazy” when he is undressed, and that 1% hydrocortisone has not helped at all.

At first glance, the discoid pattern of AE may look more like a fungal infection or psoriasis. Instead of ill defined



Figure 4 Relatively well demarcated circular patches of eczema in an infant demonstrating the discoid pattern of atopic eczema—often confused with ringworm or psoriasis.

erythema, fig 4 shows thick, circular, and arcuate patches of crusted eczema. This pattern of eczema, when seen in children, is almost always associated with concurrent flexural AE elsewhere in the body, or a history of typical flexural involvement at some stage in the past. Apart from the propensity to misdiagnose the discoid pattern of AE as something else, the other important point to note is that the treatment of thick patches of discoid eczema requires potent topical steroids for around two weeks to clear. Using 1% hydrocortisone on discoid eczema is unlikely to help. Discoid eczema often becomes infected, or is associated with more typical infected eczema elsewhere which requires appropriate treatment with systemic antibiotics. After clearing, discoid eczema commonly results in dark or lightened post-inflammatory patches in pigmented skin, which parents often misinterpret as “scarring”. Peter’s discoid eczema responded well to a potent steroid ointment applied once daily for 10 days, and he then returned to regular emollients.

PHOTOTHERAPY AND SYSTEMIC TREATMENTS

In most cases, AE can be controlled with emollients and topical treatments alone, and difficulties with disease control are often related to under-treatment or inadequate supplies rather than failure of conventional topical treatment. However, in a small number of children with very severe AE, it can be necessary to use either phototherapy with ultraviolet (UV) light or systemic immunosuppressive treatments. UV light may be useful because of its anti-inflammatory and immunomodulatory effects, especially narrow band UVB (312 nm). Most studies are small, have been performed in adults, and are not well reported.³

Other systemic drugs, such as cyclosporine and azathioprine, have been reported to be effective treatments for AE, but concerns about side effects remain.³ Prednisolone can help in severe acute exacerbations, but its long term use is restricted by side effects. All the above require careful supervision and growth monitoring, and consideration of either phototherapy or systemic treatments warrants a referral to a dermatologist.

RELEVANT LINKS

- ▶ National Eczema Society (<http://www.eczema.org>)
- ▶ British Association of Dermatologists (<http://www.bad.org.uk/>)
- ▶ Eczema Helpline 0870 241 3604
- ▶ National Institute for Clinical Excellence (www.nice.org.uk)
- ▶ Systematic review of treatments for atopic eczema. *HTA Monographs 2000*; 4 (37). (<http://www.hta.nhsweb.nhs.uk/execsumm/summ437.htm>)
- ▶ The Cochrane Skin Group (www.dermatology.ac.uk/~muzd)

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Conflict of interest: none

Although not initially commissioned for Education and Practice, we feel that the topic, format, and quality of this paper is a helpful addition to this series—the Editors

The pictures appearing in this article are derived from the authors' clinical collection and are used for illustrative purposes only; they are not related to the specific cases discussed

Annual courses for paediatricians with an interest in dermatology are held in Birmingham, Liverpool, and Dundee

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Herbal preparation to prevent respiratory tract infections

Ten years ago annual expenditure on herbal medicines was over 2 billion dollars in the USA and over 40 million pounds in the UK. Since then sales have grown by 10–15% per year. A study in Israel (Herman A Cohen and colleagues. *Archives of Pediatrics and Adolescent Medicine* 2004;**158**:217–21) of a preparation containing echinacea, propolis, and vitamin C has shown a remarkable protective effect against respiratory tract symptoms in children.

The preparation (Chizukit) contains 50 mg of echinacea (*E purpurea* upper parts, *E angustifolia* roots), 50 mg of propolis, and 10 mg of vitamin C in one millilitre. Echinacea is considered to be an immune stimulant and in vitro and animal studies have shown effects on cytokines, macrophages, and natural killer cells. Propolis is found in beehives and is said to have anti-infective properties. Vitamin C has immunomodulatory properties.

In a double-blind trial 430 children aged 1–5 years were recruited from 10 primary care community clinics and randomised to take either Chizukit or placebo for 12 weeks during the winter of 1999–2000. Parents recorded respiratory symptoms on diary cards and follow up visits were conducted at 4, 8, and 12 weeks. Any upper respiratory tract infections were confirmed by study physicians at the time of occurrence. There was a large dropout rate (55 from the treatment group and 44 controls) largely because of unpleasant taste. Among children remaining in the trial the total number of episodes of respiratory illness was 138 in 160 children (Chizukit) and 308 in 168 children (placebo). The total number of illness days was 423 vs 1040. The mean duration of episodes was 1.6 vs 2.9 days. Reductions of 50–68% were seen in diagnoses of upper respiratory tract infection, acute otitis media, pneumonia, and tonsillopharyngitis.

In an analysis of the paper (ibid: 222–4) methodological faults are highlighted. These include the large dropout rate resulting in a change from the intended intention-to-treat to per-protocol analysis, the lack of demographic data comparing treatment and control groups, and the lack of clearly defined diagnostic criteria. Nevertheless, their final comment is that the magnitude of the results is compelling and warrants further research.

Rachel was diagnosed with acute lymphoblastic leukaemia (ALL) at 6 years of age, and treated on the UKALL XI protocol¹ with randomisation to high dose methotrexate plus third intensification. She relapsed 22 months after the initial diagnosis and received further chemotherapy and a matched unrelated donor bone marrow transplant (BMT). Her conditioning for the BMT included cyclophosphamide and total body irradiation (TBI) (eight fractions of 180 cGy each). She developed graft versus host disease post-transplant and was treated with high dose methylprednisolone for five weeks and oral prednisolone for several weeks thereafter. One year after BMT she continued to be in remission from her leukaemia.

COMMENT

▶ Bone marrow transplant, especially when TBI is part of the conditioning regimen, is associated with both endocrine and non-endocrine co-morbidity (table 1).² Dividing the total dose of irradiation into smaller fractions (fractionation) is used to minimise these late effects of treatment. High dose corticosteroids, used to treat graft versus host disease, heighten the risk of iatrogenic adrenal suppression. Recovery of adrenal function usually occurs with time but this is not universal and steroid replacement therapy is sometimes needed. Therefore, after stopping steroid treatment the pituitary–adrenal axis should be assessed with a Synacthen test in all children treated with steroids for graft versus host disease, and replacement steroid therapy given if appropriate.

At 9 years of age Rachel is referred to the BMT follow up clinic for ongoing monitoring for evolving sequelae of treatment. It is now just over one year after her transplant. Routine blood tests taken as part of her annual review included thyroid function tests. The results were: free thyroxine (FT₄) 8.8 pmol/l (normal range: 10.8–18.7 pmol/l); thyroid stimulating hormone (TSH) 12 mlu/l (normal range: 0.5–4.5 mlu/l).

Although Rachel has no clinical features of hypothyroidism, the abnormal thyroid function results come as no surprise since peripheral hypothyroidism (high TSH and low FT₄) caused by radiation damage to the thyroid gland is a recognised complication of TBI (table 2). Thyroxine replacement therapy is commenced.

COMMENT

▶ There are concerns, supported by animal work, that a persistently raised TSH may increase the risk of thyroid neoplasia in a predisposed gland.³ Thyroxine replacement therapy should therefore be instituted if the TSH is persistently raised with an aim of keeping the TSH suppressed. There is also an increased risk of thyroid carcinoma caused by irradiation of the gland.⁴ Annual thyroid function tests and neck palpation should therefore be part of ongoing surveillance in all survivors of BMT regardless of the conditioning regimen.

Three months later, during a routine appointment, Rachel complains of worsening respiratory symptoms. In particular she has an intermittent cough that is sometimes exercise induced and occasionally nocturnal. In spite of this she remains very active and takes part in physical exercise at school and swims regularly. On examination there is no chest deformity and no clubbing. There are scattered crackles and wheeze, particularly over the left lung.

The consultant is aware that a transfer of atopy from the donor to the recipient of a BMT is well described⁵ and considers asthma in the differential diagnosis. Yet she is also conscious that radiation and chemotherapy induced lung damage can cause respiratory symptoms in survivors of BMT and a range of other childhood cancers. Her differential diagnosis therefore also includes post-radiation fibrosis, bronchiolitis obliterans, and (least likely) chronic graft versus host disease. She prescribes a pulse of oral steroids and inhaled beclomethasone, and arranges lung function tests.

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Table 1 Important treatments responsible for late effects in acute lymphoblastic leukaemia (ALL) treatment and bone marrow conditioning (a number of other chemotherapy agents are given but are lower risk for late effects)

Treatment for ALL (UKALLXI) ¹ includes:	Potential late effects include:
Anthracyclines (daunorubicin (180 mg/m ²)) Steroids	Cardiomyopathy—risk increases with increasing dose Reduced bone density Obesity
High dose methotrexate Etoposide At relapse chemo included: Anthracyclines (additional 200 mg/m ² epirubicin)	Reduced bone density Secondary leukaemia Increased risk of cardiomyopathy
Bone marrow conditioning	Potential late effects
Total body irradiation (TBI)	Second malignancy (particularly skin and thyroid) Thyroid nodules Cataracts Endocrine dysfunction (see table 2) Gonadal failure Sicca syndrome Restrictive lung defect
Cyclophosphamide	Cardiac dysfunction Potentiates cardiac effects of anthracyclines Pulmonary toxicity Gonadal dysfunction

The lung function tests show a restrictive lung defect with no significant reversibility with β_2 agonists (fig 1, table 3 and fig 2, table 4). After consultation with a respiratory physician, a chest x ray and a high resolution computed tomographic (CT) scan of the chest are performed. These reveal no evidence of bronchiolitis obliterans and are consistent with a diagnosis of pulmonary fibrosis. No further treatment was prescribed.

COMMENT

- ▶ Chemotherapy and radiation therapy (alone or combined) are associated with clinically significant pulmonary toxicity. The incidence of drug induced pulmonary toxicity ranges from 3–30%. The antineoplastic drugs commonly responsible include BCNU (bischloroethylnitrosourea), CCNU (chloroethylcyclohexylnitrosourea), and busulphan and bleomycin (although there is less evidence for this in children than in adults). Radiotherapy to any field that includes the lungs can cause pulmonary toxicity. The pulmonary toxic effects of chemotherapy are usefully divided into early onset, resulting in interstitial lung injury, and late onset with pulmonary fibrosis.
- ▶ Post-BMT lung toxicity is usually related to TBI rather than chemotherapy. The risk and severity of pulmonary complications following irradiation are influenced by the total dose, dose fractionation, and irradiated lung volume. Acute irradiation injury (uncommon post-BMT) typically occurs two weeks to three months after treatment and is usually limited to the irradiated field. Spirometry is the first line investigation and provides an indication of whether the lung defect is obstructive or restrictive. Radiation induced lung damage classically causes a restrictive defect with small, stiff lungs.
- ▶ Bronchiolitis obliterans is a rare disease of small airways that results in progressive dyspnoea and airflow restric-

Table 2 Endocrinopathy after bone marrow transplant

Endocrinopathy	Risk factors
Short stature	▶ Total body irradiation ▶ Previous cranial radiation ▶ Growth hormone deficiency ▶ Chronic graft versus host disease ▶ Poor nutrition/malabsorption
Growth hormone insufficiency	▶ Total body irradiation ▶ Previous cranial radiation
Thyroid dysfunction	Hypothyroidism ▶ Females ▶ Total body irradiation ▶ Busulphan/cyclophosphamide conditioning (lower risk than total body irradiation) Thyroid nodules ▶ Females ▶ Younger age at treatment Hyperthyroidism (rare) ▶ Total body irradiation Thyroid cancer ▶ Increased time from treatment ▶ Younger age at treatment ▶ Females
Gonadal dysfunction	Female ▶ Older age at treatment ▶ Total body irradiation ▶ Busulphan Male ▶ Radiation ≥ 4 Gy—azoospermia very likely ▶ Radiation ≥ 20 Gy—Leydig cell failure likely (testicular boost for testicular relapse is 24 Gy) ▶ Busulphan ▶ Effect of age unclear
Adrenal insufficiency	▶ Chronic graft versus host disease
Reduced BMD	▶ Hypogonadism ▶ Chronic graft versus host disease ▶ Inactivity ▶ Poor nutrition ▶ Growth hormone deficiency ▶ Previous chemotherapy/radiotherapy
Metabolic syndrome	▶ Risk factors unknown ▶ Total body irradiation probably important ▶ ?Role of growth hormone deficiency ▶ Hypothalamic dose ≥ 51 Gy ▶ Physical inactivity (for example, neurological impairment) ▶ Endocrinopathy

BMD, bone mineral density.

tion.⁶ It is well described after BMT as well as after lung, and heart–lung, transplantation. It can also occur as a complication of certain pulmonary infections, adverse drug reactions, toxic inhalation, and autoimmune disorders. In transplant related bronchiolitis obliterans, the diagnosis is suggested by obstructive changes (not reversible with β_2 agonists) on lung function tests. Hypoxia with exertion is also common. High resolution CT is valuable in diagnosing and assessing the severity of bronchiolitis obliterans. Prompt diagnosis is important since early treatment with high dose steroid is indicated.

As part of the evaluation of her breathlessness, Rachel also had an echocardiogram. This showed slightly

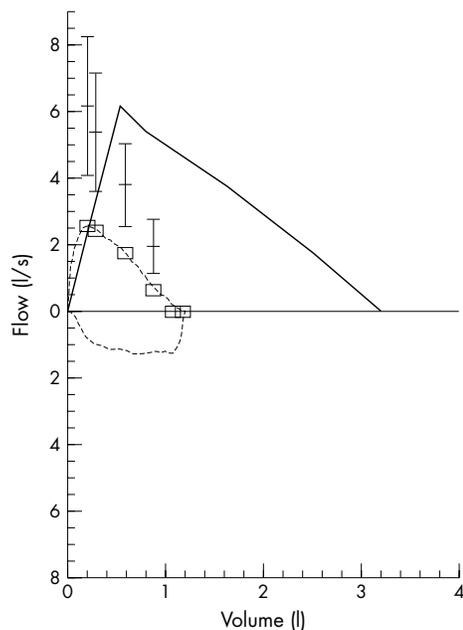


Figure 1 Lung spirometry showing a restrictive pattern. Note the normally shaped, but proportionately reduced, flow–volume loop. Flow is on the y axis, with expiratory flow in an upward direction. Volume is on the x axis, with full inspiration at 0, and full expiration at the right hand limit of the loop. Predicted loops for height, age, and sex are shown by the bold line, and error bars show the normal ranges for peak expiratory flow, and flow at 25%, 50%, and 75% of expired volumes.

Table 3 Figure 1 data: FEV₁/FVC is normal at 92%

	Actual	% predicted
FEV ₁	1.09	40%
FVC	1.18	37%
FEV ₁ /FVC%	91.9	109%
PEF	2.57	42%
FEF25	2.43	45%
FEF50	1.76	46%
FEF75	0.65	33%

Note similar reduction in volumes and flows when assessed by % predicted.
FEF, forced expiratory flow; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow.

reduced left ventricular contractility and a reduced fractional shortening (30% as compared with 36% on a previous scan). Mild septal hypokinesia was also noted.

Although the clinicians are aware of the cardiotoxic effects of Rachel's leukaemia treatment, they considered that the echocardiographic changes were not contributing to her respiratory symptoms and that continued surveillance only was necessary. It was decided to repeat her echocardiogram one year later.

COMMENT

- ▶ Anthracyclines at doses > 300 mg/m² are associated with an 11-fold increased risk of clinical heart failure, compared with a cumulative dose < 300 mg/m².⁷ There is, however, no safe dose of anthracyclines although the higher the cumulative dose the greater the risk of cardiomyopathy, with younger age at treatment and female sex being independent risk factors.⁸ They cause myocyte death and impede the return of the cardiac muscle to the resting state, thereby leading to hypertrophy of the remaining cells, interstitial fibrosis, and

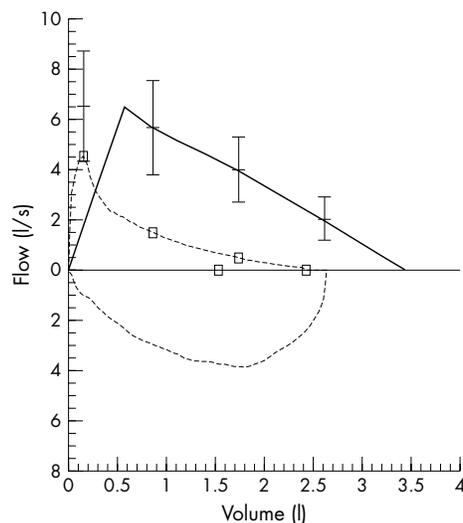


Figure 2 Lung spirometry showing an obstructive flow volume loop. Note the concave shape of expiratory flow, and disproportionate reduction in flow compared to volume.

Table 4 Figure 2 data: FEV₁/FVC is reduced to 63%

	Actual	% predicted
FEV ₁	1.53	53%
FVC	2.43	70%
FEV ₁ /FVC%	63.2	75%
PEF	4.53	69%
FEF25	1.48	26%
FEF50	0.49	12%
FEF75	Unrecordable	

reduced wall thickness. In patients who have received anthracyclines, the risk of cardiotoxicity is increased by mediastinal radiation, uncontrolled hypertension, and exposure to other chemotherapeutic agents (especially cyclophosphamide, dactinomycin, mitomycin C, dacarbazine, vincristine, bleomycin, and methotrexate). It is also more common in females, younger children, and in those with electrolyte disturbances such as hypokalaemia and hypomagnesaemia. ECG abnormalities are also relatively common, especially prolonged QT interval.

- ▶ Survivors of childhood cancer represent one of the largest new groups at risk of premature cardiovascular disease, although cardiac complications may not become manifest for many years. Factors that may precipitate cardiac decompensation are pubertal growth spurt, growth hormone treatment related growth, pregnancy, sex steroid replacement, or weight lifting. Echocardiograms at 3–5 yearly intervals (more frequently if there is concern) are recommended. Where reduced left ventricular function is demonstrated, treatment with angiotensin converting enzyme (ACE) inhibitors may be of benefit in slowing deterioration. Once end stage heart failure occurs cardiac transplantation is the only treatment option.⁹

At the next outpatient appointment Rachel, who is now nearly 10.5 years of age, is upset and depressed. It transpires that she is being teased at school for being short and fat. Her growth chart shows that she is on the 25th centile for height, 50th centile for weight,

with a median parental height (MPH) on the 75th centile. Her height velocity during the previous six months is below the 25th centile. On examination she is relatively overweight with increased abdominal girth. Her pubertal staging is Tanner stage B1, PH1 (pre-pubertal). Since her height velocity is below normal, anterior pituitary function testing is arranged.

Clonidine stimulation results in a peak growth hormone concentration of 9.2 mIU/l (< 10 mIU/l: severe growth hormone deficiency; 10–20 mIU/l: partial deficiency). Her luteinising hormone (LH) concentration was 2.3 iu/l and follicle stimulating hormone (FSH) 1.8 iu/l (pre-pubertal values). After discussion of the pros and cons of growth hormone therapy, Rachel is commenced on daily growth hormone injections.

COMMENT

- ▶ Impaired growth during and after BMT has a multifactorial aetiology—disturbed puberty, the direct action of chemotherapeutic drugs and irradiation on the growth plates, growth hormone deficiency, graft versus host disease and its treatment, and nutritional factors all play a role. The relative importance of TBI and chemotherapy is the subject of debate but it is likely that both are important. Spinal growth is impaired because of the effect of radiation on spinal growth plates. Cranial irradiation before BMT, reserved for those children with central nervous system leukaemia at diagnosis or relapse, increases the risk of growth hormone deficiency. Regular and accurate auxology including sitting height is essential. When there is a persistent reduction in height velocity (despite appropriate thyroid and/or sex steroid replacement) provocative growth hormone testing should be undertaken. Optimisation of nutrition is also important.
- ▶ If growth hormone deficiency is confirmed, replacement therapy should be considered on an individual basis not only to optimise growth but also because of the importance of growth hormone for bone health, quality of life, and cardiovascular wellbeing. The evidence suggests that the risk of relapse or secondary cancer is not significantly increased by growth hormone replacement therapy.⁸ IGF-1 should be monitored and maintained within the normal age related range.

Rachel grows very well during the next two years on growth hormone replacement therapy. However, when reviewed at the age of 12 years 9 months, she is noted to have had a reduced height velocity during the preceding six months. The general examination is normal, and pubertal staging is B1 and PH 1. There is no family history of pubertal delay. Measurement of LH, FSH, and oestradiol show menopausal gonadotrophin concentrations (LH 55 iu/l, FSH 105 iu/l, oestradiol < 75 pmol/l).

Since Rachel is almost 13 years of age with no clinical signs of puberty and no family history of pubertal delay, the paediatrician is concerned that she may have ovarian failure and this is confirmed by the investigations. It is therefore decided that oestrogen replacement therapy should be started.

Normally, investigations are indicated only where there are no signs of puberty by 14 years of age, but in this case Rachel has clear risk factors for ovarian failure.

COMMENT

- ▶ The risk of gonadal dysfunction after BMT is high following TBI or busulphan/cyclophosphamide conditioning.¹⁰ In females, older age at transplantation increases the risk of ovarian failure and reduces the likelihood of ovarian recovery. Regular monitoring (3–6 monthly) of physical signs and gonadotrophin concentrations (annually) is required around the age of puberty.
- ▶ In primary and secondary gonadal failure appropriate sex steroid replacement therapy is necessary. Ovarian failure may be temporary, particularly in younger children and with lower doses of radiation, so discontinuation of oestrogen replacement for 6–8 weeks every two years should be considered to determine whether ovarian function has recovered. Ovarian failure after TBI (14.4 Gy) is unlikely to be reversible¹¹ Pregnancy after BMT is well described but there is an increased risk of second trimester miscarriage and fetal growth restriction, probably because of radiation induced impairment of uterine blood flow and elasticity.
- ▶ In males, TBI affects germ cells more than Leydig cells.⁸ Thus, although oligospermia or azoospermia (and hence infertility) are common post-BMT, preservation of Leydig

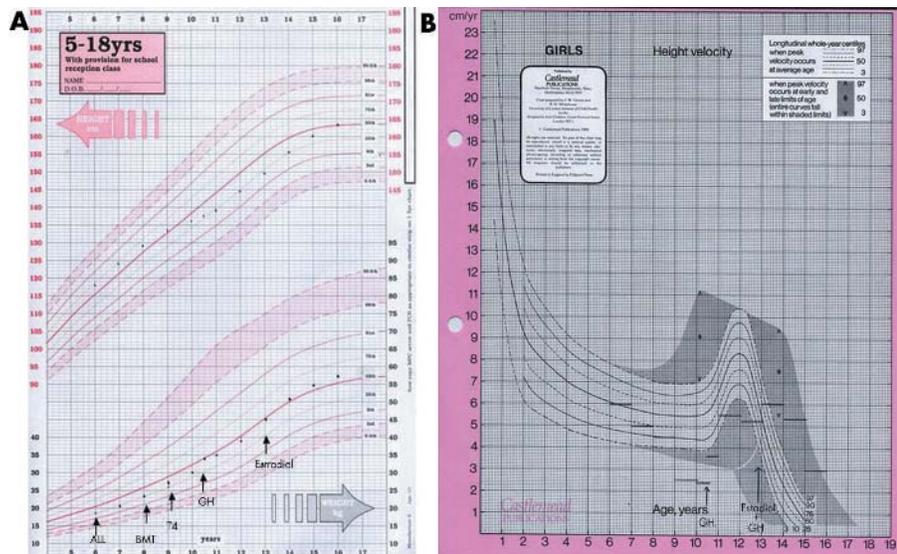


Figure 3 (A) Rachel's growth chart showing her final height at 16 years on the 50th centile and weight between the 50th and 75th centile. (B) Rachel's height velocity chart depicting the points where she started her growth hormone (GH) treatment and her oestrogen (Estradiol) replacement added on at 12 years and 9 months. After addition of both treatments her height velocity improved. ALL, acute lymphoblastic leukaemia; BMT, bone marrow transplant; GH, growth hormone; T4, thyroxine.



Figure 4 Cataract following total body irradiation.

cell function may maintain testosterone secretion within the normal range despite raised LH and FSH concentrations. The testes post-BMT are often inappropriately small

Table 5 Bone marrow transplant follow up protocol

Auxology including sitting height	3–6 monthly
Bone age	Plot BMI Annually
Discussion points	Schooling/employment—statementing? Psychology assessment Weight Diarrhoea? Eyes and mouth—?Sicca syndrome (Consider faecal elastase/trial of Creon if loose stools/poor weight gain) Hip pain/knee pain: consider MRI— ?osteonecrosis Fertility—if relevant/appropriate age
Special points on examination	Pubertal assessment at each visit (testicular volume not a useful indicator of pubertal progression) Palpation of thyroid Check moles Neurological examination Fundoscopy (cataracts) Blood pressure
Echocardiogram	All patients who have had anthracyclines Echocardiogram at end of treatment (Request FS, LV function, septal motility) ECG annually (QT interval) 3 yearly if FS $\geq 30\%$, annually if $< 30\%$ Evaluate if persistent poor growth
Growth hormone status	Annually—as increased risk of metabolic syndrome
Glucose:insulin ratio	GTT if abnormal
Lipids	Fasting lipids annually
Thyroid function	T4 and TSH annually Replace thyroxine if TSH persistently elevated
Gonadotrophins	LH, FSH, oestradiol/testosterone annually after 10 years of age Consider pelvic USS in females; uterine size, endometrial thickness, Doppler studies Semen studies in males as requested by patient Ovarian failure may be reversible—trial off oestrogen for 6–8 weeks every 2 years recommended
Evaluation of BMD	Annual PTH and vitamin D DEXA at 2 years, then 3 yearly if concern (must correct for size)

BMD, bone marrow density; BMI, body mass index; DEXA, dual energy x ray absorptiometry; ECG, electrocardiogram; FS, fractional shortening; FSH, follicle stimulating hormone; GTT, glucose tolerance test; LH, luteinising hormone; LV, left ventricle; MRI, magnetic resonance imaging; PTH, parathyroid hormone; TSH, thyroid stimulating hormone; USS, ultrasound scanning.

and soft (because of radiation and/or chemotherapy damage to germ cells) and hence testicular enlargement should not be used to monitor pubertal progression.

Rachel is now 15.5 years and recently had her first oestrogen withdrawal bleed. Oestrogen replacement therapy has resulted in breast stage 4. She is pleased with her height, which is between the 25th and 50th centile (fig 3) and has settled well in school. Examination is normal other than small cataracts that are not impairing her vision (fig 4). Nevertheless, she has been referred to an ophthalmologist for a formal assessment. She continues to be monitored annually in respect of the late effects of her leukaemia and its treatment.

COMMENT

- ▶ Cataracts may occur following TBI and although they may be present for many years without visual impairment, surgery is occasionally required. They are one of many initially asymptomatic complications that mean that lifelong surveillance is required for all BMT survivors.
- ▶ A vital component of follow up, often delivered by nurse specialists, is health promotion. Particular issues include dietary and lifestyle promotion of bone health (because of an increased risk of osteopenia and osteoporosis) and sun protection (because of increased risk of skin cancer). Counselling in relation to smoking is also important, especially where there is already established lung disease such as pulmonary fibrosis. Table 5 provides a suggested follow up protocol for bone marrow survivors. As additional late effects become evident such protocols will need to be modified. For example, there is growing evidence of an increased risk of insulin resistance and metabolic syndrome following BMT.¹² Monitoring of the glucose:insulin ratio and blood lipid values, with an oral glucose tolerance test if the glucose:insulin ratio is abnormal, has therefore been added to our follow up protocol.
- ▶ This case shows the wide ranging nature of the late sequelae of childhood cancer treatment. Almost any system can be affected, with cardiac, respiratory, and particularly endocrine sequelae being common.^{2 13 14} It also demonstrates that, despite considerable late morbidity, many patients have good quality of life. In addition, historically very few patients with relapsed leukaemia like Rachel would have achieved long term cure, highlighting the massive improvement in survival for childhood leukaemia that has been seen in the last 30 years.

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IMAGES IN PAEDIATRICS.....

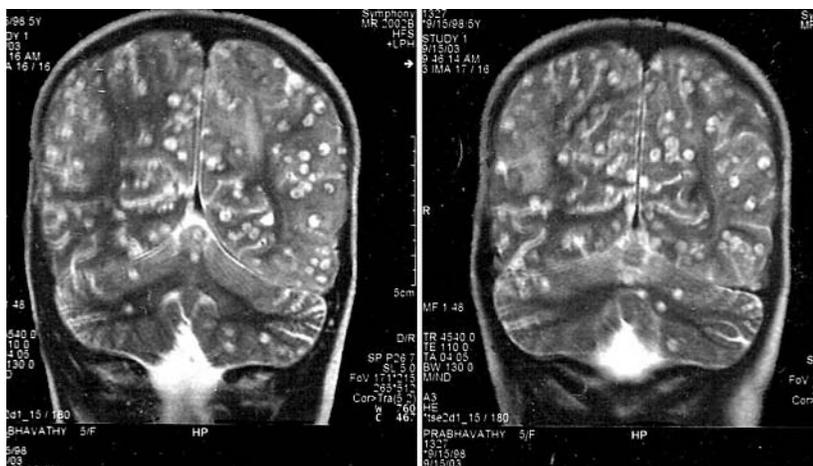
doi: 10.1136/adc.2004.066795

Starry sky: multiple neurocysticercosis

A 5 year old developmentally normal girl, with seizure disorder for one year, presented with altered sensorium and quadriparesis. Magnetic resonance imaging of the brain showed a starry sky pattern with multiple rounded calcific lesions. Both serum and cerebrospinal fluid were positive for cysticercus serology. Work up for tuberculosis was negative. The girl was treated with albendazole and steroids, and the seizures were controlled with anticonvulsants.

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CORRECTION

doi: 10.1136/adc.2004.050237corr1

C Flohr and H C Williams. Evidence based management of atopic eczema. *Arch Dis Child Ed Pract* 2004;**89**:ep35-9. Due to a production error Figure 1 was missing from the print version of this article. The illustration and caption are reproduced below. A corrected version of the article can be downloaded from the website <http://ep.bmjournals.com/cgi/reprint/89/2/ep35>.

The error is regretted.



Figure 1 Widespread, poorly demarcated redness with associated surface dryness typical of atopic eczema in a young child.