Hong Kong J. Dermatol. Venereol. (2014) **22**, 66-74

Paediatric Dermatology Column: Review Article

The use of systemic therapy in childhood eczema: a review and our Australian experience

系統性治療在兒童濕疹之應用：澳洲的經驗回顧

VM Palmer and D Orchard

Topical therapies and patient education are the mainstays of treatment for atopic dermatitis, being effective for the majority of children who have limited disease of mild to moderate severity. More severe, widespread, or recalcitrant disease may necessitate systemic therapy. Treatment modalities may be divided into education, topical therapies, antihistamines, antimicrobials, systemic vitamin D, phototherapy, systemic steroids and systemic immunomodulatory agents. This review will focus mainly on the more commonly used systemic therapies in paediatric dermatology and also give advice based on our experience.

外用藥物治療和患者教育是治療異位性皮膚炎的基石，對大多數輕微至中度嚴重性的兒童異位性皮膚炎皆爲有效。但更嚴重的、廣泛的或頑固的病情，便可能要考慮系統性治療。治療方法一般可分爲病者教育、外用療法、抗組織胺、抗微生物藥物 、口服維生素 D 、光療、系統性類固醇激素和系統性免疫調節劑。本回顧文章將主要集中在小兒皮膚科中比較常用的系統性治療藥物，並根據我們的經驗提出用法建議。

Keywords: Atopic dermatitis, paediatric, systemic treatment

關鍵詞：異位性皮膚炎、小兒科、系統性治療

Introduction

Atopic dermatitis (AD) affects 10-20% of children worldwide,[1] with 28% of infants in Australia reported to suffer from eczema by 12 months of age.[2] Atopic dermatitis places a significant burden on affected children and their families.

Atopic dermatitis is a cutaneous inflammatory reaction pattern, and individuals have varying thresholds dependent on the skin barrier function, susceptibility genes, immune function, and the environment, creating a broad range of clinical presentations. The two strongest associated risk factors for the development of AD are 1) family history of atopy and 2) loss of function mutations in the filaggrin (FLG) gene.[3] There are many potential triggers, and most

Skin and Cancer Foundation, Victoria, Australia
VM Palmer, BSc, MBBS

Royal Children's Hospital, Melbourne, Australia
D Orchard, MBBS, FACD

Correspondence to: Dr. Vanessa M Palmer

Skin and Cancer Foundation, Level 1, 80 Drummond Street, Carlton, Victoria, 3053, Australia

eczema presentations are multifactorial. Common triggers include dryness, heat, irritation, infection, allergy, intolerance or other immune stimuli.

Most patients respond well to the addressing of triggers and topical therapies including emollients, topical corticosteroids and topical calcineurin inhibitors, however a minority of children have resistant disease that requires a systemic approach. Safety of topical corticosteroid use has been extensively examined which is why they remain as the pivotal first line agent to settle eczema.[4-6] Further review of topical therapies is beyond the scope of this article, which will focus on systemic therapies.

Treatment must be individually tailored, depending on age, site, morphology, extent, previous treatment and the presence or absence of secondary infection. Emollients form the basis of management, and should be used even when the skin is clear. Worsening of eczema is often due to bacterial super-infection and treatment with antibiotics (topical or systemic) is warranted. Educational programmes play a crucial role in eczema management for the patients and their families. An updated Cochrane review detailed potential gains of education programmes; although lacking rigorously designed studies, education may be especially important for parents of children under seven years old.[7] The effectiveness is also directly linked to patient adherence to the application schedule, so the treatment must be acceptable to both the patient and caregiver.

Discoid, or nummular, eczema is of unknown aetiology, and starts with eczema at one site for any reason, usually in minimally atopic patients. The skin then breaks out in 'sympathy' patches, and becomes a vicious cycle. The rationale of therapy is to break the cycle, by preventing pruritus and maintaining a barrier function.

The aim of this paper is to review the systemic therapies.

Antihistamines

Although commonly prescribed for eczema-associated pruritus, a recent Cochrane review found no evidence to support the efficacy or safety of oral H1 antihistamines as monotherapy for children and adults with AD. A further review assessing efficacy as adjunct therapy is ongoing.[8] In our experience antihistamines are useful in select patients with symptomatic dermographism.

Antimicrobials

Interventions to reduce *Staphylococcus aureus* in the management of AD were the subject of a recent Cochrane review and update.[9,10] No convincing evidence for anti-staphylococcal interventions in patients with eczema that was not clinically infected was found. Of note the European TREatment of severe Atopic eczema in children Taskforce (TREAT) survey found that over half of the respondents routinely test and treat skin infection prior to initiation of systemic immunomodulatory agents, with the majority of clinicians opting for penicillins as the first-line.[11] Certain individuals with eczema do seem to be particularly susceptible to secondary colonisation and infection. The use of bleach baths,[12] and at times prophylactic oral antibiotic therapy for some individuals is important.

Systemic vitamin D

Vitamin D as therapy has been a popular topic of research in recent years, and stimulated much debate. Recent literature reviews have shown that replenishing deficient vitamin D levels in AD patients improves disease severity, with many studies showing an inverse relationship between AD severity and vitamin D levels.[13] A Cochrane review in 2012, however, found no convincing evidence that dietary supplements were of benefit in established atopic eczema.[14]

Phototherapy / UV therapy

Narrowband UVB (nbUVB) (311 nm) is the preferred choice for full-body phototherapy in children as it is less erythemogenic and is the most efficient anti-inflammatory wavelength.[15] It is also easier to deliver than psoralens and UVA (PUVA) which although proven to be efficacious in children, requires the strict use of protective eyewear for 24 hours. A comparative cohort study in children treated with twice weekly nbUVB for a total of 24 exposures (n=29) reported a 61% reduction in mean six area, six sign atopic dermatitis (SASSAD) score compared to a 6% increase in the unexposed cohort (n=26). This was associated with improved quality of life scores and maintained clinical effect for 6 months post treatment.[16] A retrospective evaluation of nbUVB safety and efficacy in the treatment of psoriasis and AD in 129 paediatric patients found that 25% (9 of 36) of patients with AD cleared with the treatment, and 41% (16 of 36) had a partial response. Adverse effects in children with AD treated included six cases of mild erythema, one case of first-degree burn and three cases of pruritus. The authors advised annual follow-up for carcinoma surveillance.[17] Narrowband UVB is an appropriate second-line therapy for eczema that requires much effort and copious topical corticosteroids to maintain, and may delay or prevent the need for immunomodulatory drugs. Contraindications include inability to attend for regular treatment, inability to stand in a confined space, fair skin or family history of skin cancer, and prolonged use with regard to the total UVB exposure. Long-term risk of skin cancer (particularly in Caucasian children) needs to be seriously considered, especially with children that may go on to receive systemic immunomodulatory treatment that further increases the risk of cutaneous malignancies.

Systemic treatments

Oral immunomodulatory treatments are indicated for chronic life-ruining eczema, and for AD patients whose families are in desperation. The aim of treatment is to provide respite and hopes to break the vicious cycle. Prior to initiating oral immunomodulatory treatments, it is important to rule out remediable reasons for the failure of first-line agents or exacerbating factors. It may also be prudent to have an observed hospital stay to ensure a failure in education or application techniques is not to blame for the treatment failure. There are no official prescribing guidelines for systemic agents in children with AD, and there is much variability between centres in monitoring recommendations. An update from our centre was published in 2008,[18] and there have been other recent reviews on this topic. [19,20]

Prednisolone

Prednisolone, when necessary, is best used in very short bursts given the side effect profile of longer term use (see Table 1). It is useful for treating allergic reactions, especially severe type-1 or type-4 allergic reactions, in kick-starting therapy for severe eczema or discoid eczema, or to use at times when rapid clearance is important, such as for school examinations or camps. The usual starting dose is 1 mg/kg for 3 days, then weaned over 10 days. It is important to note that if oral prednisolone is taken at dosages of ≧20 mg/day, ≧2 mg/kg/day, for 14 days or longer, then live vaccinations are contraindicated during the subsequent three months.[21] Children with concomitant asthma have often received previous courses of oral or inhaled corticosteroids, and clinicians should be wary of prescribing further courses in these patients due to cumulative risks.

Cyclosporin A

Cyclosporin A is a calcineurin and IL-2 inhibitor, and potently inhibits T-lymphocyte dependent immune responses. Cyclosporin was recently found to be the most common systemic treatment

Table 1. Indications, screening and monitoring advice for systemic agents in childhood atopic dermatitis[18]

Therapy	Mechanism of action	Advice/ uses	Screening Tests	Monitoring	Dose	Advantages	Contraindications/ considerations	Side effects short term	Side effects long term
nbUVB (311 nm)	Immuno-modulatory via inhibition of Langerhan's cells and alters keratinocyte production Also reduces *Staphylococcus aureus* colonisation	Eczema reasonably controlled but taking a lot of effort and topical steroids Type IV or V skin	Full skin examination	Clinic review Ongoing annual full skin examination	Most common initial dose is 70% of minimal erythema dose (MED) Usually 2-3 times a week for 12 week course or until clearance MEDs >390 mJ/ cm^2 are more likely to clear	May delay or avoid the need for systemic immune-modulatory agents Helps to decrease time-consuming topical regime	Logistics Ability to stand in confined space Fair skin Family history of skin cancer Prolonged use (consider total UVB exposure) and need for further immune-modulatory therapy in future	Erythema Pruritus Pain Burn Initial flare Photosensitivity Pigmentation Hypertrichosis Herpes simplex reactivation Koebnerisation	Premature skin-aging Cumulative risk of skin cancer unknown
Prednisolone	Anti-inflammatory effects via decreased production of cytokines and pro-inflammatory molecules and effects on specific inflammatory cells	Allergic reactions To 'kick start' therapy for severe eczema or discoid eczema To use on school camps/ examination times Use in very short bursts	Usually none for short term use	Usually none for short term use	Usually 1 mg/kg for 3 days then wean down over 10 days	Extremely effective Rapid response Short-term tolerability Low cost Availability	Consider previous corticosteroid use (topical, inhaled, previous oral prednisolone courses) Long-term side effects unacceptable Corticosteroid dependency	Hypothalamic-pituitary-adrenal axis Steroid withdrawal syndrome Addisonian crisis Metabolic effects Hyperglycaemia, hypertension Congestive heart failure Cushingoid changes Increased appetite, excessive weight gain Hypokalaemia, hypertriglyceridaemia Hypocalcaemia Menstrual irregularity Osteoporosis, osteonecrosis Myopathy Growth impairment Cutaneous Flare of pustular psoriasis Poor healing Striae, atrophy, telangiectasia Steroid acne, actinic purpura Infection Telogen effluvium, hirsutism Acanthosis nigricans Gastrointestinal Nausea, vomiting, steato-hepatitis Peptic ulcer disease Gastro-oesophageal reflux Bowel perforation Ocular Cataracts, glaucoma Refraction error, infection Psychiatric Psychosis, personality change, Depression, agitation Pseudotumour cerebri Epidural lipomatosis Peripheral neuropathy Infectious Tuberculosis reactivation Herpes virus Opportunitistic infections Malignancy Non-Hodgkin's lymphoma Kaposi's sarcoma Squamous cell carcinoma (skin, female genito-urinary tract)	

(continued on page 70)

Table 1. Indications, screening and monitoring advice for systemic agents in childhood Atopic dermatitis[18] (cont'd)

Therapy	Mechanism of action	Advice/ uses	Screening Tests	Monitoring	Dose	Advantages	Contraindications/ considerations	Side effects short term	Side effects long term
Cyclosporin A	Calcineurin inhibitor (interleukin-2 inhibitor)	For children who have a protracted flare and/or poor social situation, with a mild-moderate background eczema tendency For severe combined chronic urticaria with eczema	Blood pressure Blood tests at baseline: full blood count, renal and liver profiles	Blood pressure 2 hours post cyclosporin levels (aim for 400-1000 µg/L) Blood tests (full blood count, renal and liver profile) at 1 month, then every 3 months	Maximum 5 mg/kg in divided doses Wean down with control Aim for 3-9 month course	Well-tolerated Convenient syrup Reasonably quick acting Usually achieves adequate control Children tend to tolerate better than adults	Renal impairment Eczema will often flare upon weaning	Renal dysfunction Hypertension Headache Tremor, paraesthesia and hyperaesthesia Arthralgia and myalgia Hypertrichosis Nausea and vomiting Gingival hyperplasia Hyperkalaemia Hyperuricaemia Hypomagnesaemia Hyperlipidaemia	Lymphoma Internal malignancy Skin cancer Chronic renal disease (arteriolo-pathy and tubular interstitial disease)
Azathioprine	Purine analogue Anti-inflammatory and immune-suppressive effects	For chronic severe patients with massive IgE levels	Blood tests at baseline: Full blood count (note lymphocytes are sensitive, aim for range 1.0-1.5x10^3/µl) Renal and liver profiles, IgE (very high >2000 units/mL usually with environmental allergies) TPMT (1% of population have homozygous deficiency: have much higher risk of myelo-suppression)	Blood tests: Full blood count, renal and liver profile at 1 month and then every 3 months	Aim for 2.5 mg/kg/day (dependent on TPMT level: TPMT <3 nmol/h/mL: contraindicated, TPMT 3-8nmol/h/mL: low dose 0.5-1mg/kg/day, TPMT 8-14.5 nmol/h/mL: 1-3 mg/kg/day allowed) Incremental dosage increase (start at 25% to 33% of full dose and increase to full dose over 6-8 weeks)	Has continued effect even after cessation Many patients are able to be weaned successfully May not be as immunosuppressive as cyclosporin A	Delayed onset of action: up to 12 weeks after full dose reached	Hypersensitivity reactions (within 1-4 weeks of initiation) including: fever, malaise, rigors, myalgia, cardiovascular collapse, pneumonitis cutaneous eruptions (maculopapular rash, urticaria, vasculitis, erythema multiforme, erythema nodosum) Pancytopaenia Nausea, vomiting Diarrhoea	Malignancy including Non-Hodgkin B-cell lymphoma Squamous cell carcinoma of skin Opportunistic infections including Herpes simplex Herpes zoster Human papilloma-virus Molluscum contagiosum Teratogenicity
Methotrexate	Inhibits dihydrofolate reductase More anti-inflammatory than immuno-suppressive	Useful in recalcitrant discoid eczema and those not responding or intolerant to cyclosporin A and azathiaprine	Blood tests at baseline: Full blood count Renal and liver profiles	Full blood count, renal and liver profiles at 1 month and then every 3 months	At rheumatological doses: 0.3-0.6 mg/kg/week MUST also take Folic Acid 5 mg weekly	Well-tolerated Safer than other immuno-suppressants	Not as powerful	Haematological toxicity: pancytopaenia Nausea, Vomiting Stomatitis Hepatotoxicity Idiosyncratic pulmonary toxicity (acute pneumonitis, pulmonary fibrosis) Renal toxicity Headache Fatigue Dizziness Cutaneous effects including acral erythema, epidermal necrosis, vasculitis, alopecia and phototoxicity	Lymphoma Teratogenicity Methotrexate osteopathy

for children with severe AD in the TREAT survey, followed by oral corticosteroids and then azathioprine.[11] Recently, an unblended study compared the efficacy and safety of methotrexate (7.5 mg/week) and cyclosporin (2.5 mg/kg/day) over a 12-week period in 40 children with severe AD: both agents showed similar efficacy and were associated with mild and reversible side effects, none of which required dose reduction or cessation of the drug.[22] Schmitt et al undertook a systematic review and meta-analysis of cyclosporin for AD treatment: three of their included studies involved only children, with doses ranging from 2.5 to 5 mg/kg/day for durations ranging from six weeks to one year. Pooled data from the meta-analysis including adults as well found that cyclosporin was similarly effective in adults and children, with a relative effectiveness of 55% after six to eight weeks.[23]

There are no published guidelines for dosing and monitoring in children. Flohr and Irvine have recently published their advice for adults and children on systemic therapies, and recommended starting cyclosporin at 2.5 mg/kg/day, increasing to 5 mg/kg/day if necessary.[19] We start our patients on 5 mg/kg/day in divided doses, and measure cyclosporin levels two hours post dose, aiming for 400-1000 µg/L. We monitor blood pressure, full blood count, renal and liver profile pre-treatment, after one month, and subsequently every three months (see Table 1). The dose should be weaned as disease is controlled, and a total duration of therapy of 3-9 months is recommended. Cyclosporin is generally well-tolerated, especially in younger patients, and is available as a convenient syrup formulation. The onset of action is rapid, and it usually achieves adequate control, but prompt relapse after cessation is the rule. Long-term side effects include impaired renal function, immunosuppression, hypertension, hyperlipidaemia, hypertrichosis and gingival hyperplasia. We find it useful for children who experience a protracted flare and/or a poor social situation, on a background of not overly severe AD, and also for severe chronic urticaria combined with eczema.

Azathioprine

Azathioprine is a purine analogue with anti-inflammatory and immunosuppressive effects. A retrospective evaluation of azathioprine in 48 children with severe AD has shown it to be safe and effective, although in some cases a higher dosage than the usual adult dosage (2.5-3.5 mg/kg/day) was needed, possibly due to decreased drug absorption.[24] The British Association of Dermatologists' guidelines for the safe use of azathioprine advise long-term follow-up, and advise on photoprotection when using the drug off-licensed for paediatric AD.[25]

Although not reported in AD patients treated with azathioprine, the risks of lymphoma or progressive multifocal leucoencephalopathy (PML) may be especially important when receiving azathioprine in the context of inflammatory bowel disease (lymphoma) or in combination immunosuppressive therapy or in autoimmune disease (PML).[19]

Thiopurine methyl-transferase (TPMT) metabolises azathioprine to an inactive metabolite, and activity of this enzyme must be tested prior to therapy to reduce the risk of toxicity. One percent of the population has a homozygous deficiency in TPMT and are therefore at higher risk of myelosuppression secondary to increased conversion to the active metabolite, mercaptopurine. Potential problems with azathioprine include tolerability (nausea, lethargy, tiredness), hypersensitivity (seen after two to three weeks of therapy), immunosuppression and bone marrow suppression.

The target dose should be 2.5 mg/kg/day, achieved with incremental increases: start at one quarter to one third of the calculated full dose, and increase gradually over six to eight weeks. Full blood count, renal and liver profile, IgE and TPMT levels should be checked pre-treatment, then a repeat full blood count, renal and liver profile should be checked after one and three months. Dosage increases should be accompanied by

more frequent blood tests. Very high levels of IgE (greater than 2000 units/mL), are often associated with environmental allergies, this ratifies the decision to use immunosuppression but does not impact upon therapy. It is noteworthy that atopic dermatitis with other manifestations of atopy including IgE elevations was concluded to be a risk factor for childhood asthma occurrence, severity and persistence.[26]

Azathioprine has a delayed clinical effect taking up to eight to 12 weeks before improvement is seen after the full dose is reached. Lymphocyte count is the most sensitive biochemical marker of effect, and we aim for a range of 1.0 to 1.5x10^3/µl. Benefits of azathioprine include sustained efficacy, and most patients can be successfully weaned off treatment over many months. We recommend using azathioprine for patients with chronic, severe eczema with massive IgE levels.

Methotrexate

Methotrexate inhibits dihydrofolate reductase, and is more anti-inflammatory than immunosuppressive, and although the mechanism in AD is poorly understood, it is known to reduce allergen-specific T-cell activity. Rheumatological doses are 0.3-0.6 mg/kg/week and it is from the rheumatology literature that most information about this drug is derived. As previously discussed, a randomised controlled trial in 40 children found methotrexate (7.5 mg weekly) comparable in efficacy with cyclosporin (2.5 mg/kg/day).[22] Methotrexate has a delayed clinical efficacy similar to azathioprine. We often use 10 mg/week, with the option to increase to 15 mg/week if it is well-tolerated. Folic acid 5 mg/week should be given. Full blood count and renal and liver profile should be checked pre-treatment, at one month, and then every three months. Methotrexate is generally well-tolerated, with occasional nausea, liver function abnormalities and bone marrow suppression. Subcutaneous administration may ameliorate gastrointestinal upset, and can be successful in those not responding to oral therapy. In our experience, it is safer than other immunosuppressants, though not as powerful. It is useful in recalcitrant discoid eczema and those not tolerating or responding to cyclosporin or azathioprine.

Other treatment options

The remaining systemic treatment options have insufficient evidence to guide clinical practice.[27] Mycophenolate mofetil (MMF) is not funded in Australia, and may cause unwanted gastrointestinal side effects, and less commonly liver dysfunction and rarely bone marrow suppression. A retrospective chart analysis of 12 children with severe AD treated with MMF after failure to respond to, or intolerance of azathioprine reported 66% (8 of 12) of patients had significant clinical improvement, and lower rates of laboratory abnormalities when compared to children on azathioprine.[28] A retrospective analysis of 14 children treated with MMF, at doses of 40-50 mg/kg/day for younger children and 30-40 mg/kg/day for adolescents, reported that 8 of 14 patients had >90% improvement within three months of therapy initiation. All patients tolerated the medication well, and 12 patients continued treatment for up to 24 months without adverse effects.[29]

Interferon gamma may be considered as a third-line therapy option for patients with severe AD unsuitable for, or resistant to, other systemic agents. Close monitoring is required, and moderate evidence for its short-term use in adults has been discussed in a review.[30]

Use of intravenous immunoglobulin (IVIg) is limited by a high cost and limited access, and in a recent review was not recommended for treatment of severe AD due to poorer efficacy compared to placebo or cyclosporin.[30]

Roekevisch et al conducted a systematic review of safety and efficacy of systemic therapy for

moderate to severe AD in adults, and suggested pimecrolimus as a possible short-term option. They advised that montelukast, traditional Chinese herbal medicine, *Mycobacterium vaccae* (specifically reviewed in children), and thymopentin are currently not recommended for treatment of AD. Randomised controlled trials using these medications in children are lacking.

Omalizumab is an IgE monoclonal antibody that, until recently, had been sparsely reported as a treatment for children with AD. A letter reporting the use of omalizumab in seven children (aged 6-19 years) for severe AD, with doses dependent on patient's mass and baseline serum IgE titres found that all patients improved after three to six months, with IgE levels reduced by 60.5%. There were no adverse effects reported during the mean follow-up period of 30 months.[31]

The T-cell modulator, efalizumab, does not have robust enough evidence to recommend its off-label use in this population. Siegfried reported sustained efficacy in a child, though the patient developed acute autoimmune thrombocytopaenia and was forced to discontinue its use.[32]

In summary, it is important to prevent eczema from remaining severe, and be liberal with the use of topical corticosteroids, and to be aware of systemic agents for cases that require them.

References

1. Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR. Is eczema really on the increase worldwide? J Allergy Clin Immunol 2008;121:947-54 e15.
2. Martin PE, Koplin JJ, Eckert JK, Lowe AJ, Ponsonby AL, Osborne NJ, et al. The prevalence and socio-demographic risk factors of clinical eczema in infancy: a population-based observational study. Clin Exp Allergy 2013;43:642-51.
3. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: Section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70:338-51.
4. Van Der Meer JB, Glazenburg EJ, Mulder PG, Eggink HF, Coenraads PJ. The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. The Netherlands Adult Atopic Dermatitis Study Group. Br J Dermatol 1999;140:1114-21.
5. Thomas KS, Armstrong S, Avery A, Po AL, O'Neill C, Young S, et al. Randomised controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild or moderate atopic eczema. BMJ 2002;324:768.
6. Berth-Jones J, Damstra RJ, Golsch S, Livden JK, Van Hooteghem O, Allegra F, et al. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. BMJ 2003;326:1367.
7. Ersser SJ, Cowdell F, Latter S, Gardiner E, Flohr C, Thompson AR, et al. Psychological and educational interventions for atopic eczema in children. Cochrane Database Syst Rev 2014;1:CD004054.
8. Apfelbacher CJ, van Zuuren EJ, Fedorowicz Z, Jupiter A, Matterne U, Weisshaar E. Oral H1 antihistamines as monotherapy for eczema. Cochrane Database Syst Rev 2013;2:CD007770.
9. Birnie AJ, Bath-Hextall FJ, Ravenscroft JC, Williams HC. Interventions to reduce Staphylococcus aureus in the management of atopic eczema. Cochrane Database Syst Rev 2008(3):CD003871.
10. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, Williams HC. Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review. Br J Dermatol 2010;163:12-26.
11. Proudfoot LE, Powell AM, Ayis S, Barbarot S, Baselga Torres E, Deleuran M, et al. The European TREatment of severe Atopic eczema in children Taskforce (TREAT) survey. Br J Dermatol 2013;169:901-9.
12. Huang JT, Abrams M, Tlougan B, Rademaker A, Paller S. Treatment of Staphylococcus aureus colonization in atopic dermatitis decreases disease severity. Pediatrics 2009;123:e808-14.
13. Mutgi K, Koo J. Update on the role of systemic vitamin D in atopic dermatitis. Pediatr Dermatol 2013;30: 303-7.
14. Bath-Hextall FJ, Jenkinson C, Humphreys R, Williams HC. Dietary supplements for established atopic eczema. Cochrane Database Syst Rev 2012;2:CD005205.
15. Veith W, Deleo V, Silverberg N. Medical phototherapy in childhood skin diseases. Minerva Pediatr 2011;63: 327-33.
16. Darne S, Leech SN, Taylor AE. Narrowband ultraviolet B phototherapy in children with moderate-to-severe eczema: a comparative cohort study. Br J Dermatol 2014;170:150-6.
17. Pavlovsky M, Baum S, Shpiro D, Pavlovsky L, Pavlotsky F. Narrow band UVB: is it effective and safe for paediatric psoriasis and atopic dermatitis? J Eur Acad Dermatol Venereol 2011;25:727-9.
18. Borchard KL, Orchard D. Systemic therapy of paediatric atopic dermatitis: an update. Australas J Dermatol 2008;

49:123-34;quiz 135-6.
19. Flohr C, Irvine AD. Systemic therapies for severe atopic dermatitis in children and adults. J Allergy Clin Immunol 2013;132:774-774.e6.
20. Silverberg JI. Atopic Dermatitis: An Evidence-Based Treatment Update. Am J Clin Dermatol 2014 Jan 25. [Epub ahead of print].
21. National Center for Immunization and Respiratory Diseases. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2011;60: 1-64.
22. El-Khalawany MA, Hassan H, Shaaban D, Ghonalm N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. Eur J Pediatr 2013; 172:351-6.
23. Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema - a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2007;21:606-19.
24. Murphy LA, Atherton D. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. Br J Dermatol 2002; 147:308-15.
25. Meggitt SJ, Anstey AV, Mohd Mustapa MF, Reynolds NJ, Wakelin S. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. Br J Dermatol 2011;165:711-34.
26. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Gotz M, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy 2008;63:5-34.
27. McAleer MA, Flohr C, Irvine AD. Management of difficult and severe eczema in childhood. BMJ 2012;345:e4770.
28. Waxweiler W, Agans R, Morrell DS. Systemic treatment of pediatric atopic dermatitis with azathioprine and mycophenolate mofetil. Pediatr Dermatol 2011;28:689-94.
29. Heller M, Shin HT, Orlow SJ, Schaffer JV. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. Br J Dermatol 2007;157:127-32.
30. Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: A systematic review. J Allergy Clin Immunol 2013;133:429-38.
31. Lacombe Barrios J, Begin P, Paradis L, Hatami A, Paradis J, Des Roches A. Anti-IgE therapy and severe atopic dermatitis: a pediatric perspective. J Am Acad Dermatol 2013;69:832-4.
32. Siegfried EC. Long-term follow-up of a child treated with efalizumab for atopic dermatitis. Arch Dermatol 2007; 143:1077-8.