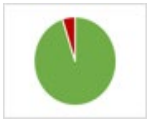
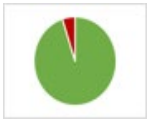
Phototherapy and Photochemotherapy

We **recommend** narrowband UVB and medium-dose UVA1 for AE patients with moderate-to-severe AE.	↑↑	>95%  (24/25) Expert Consensus
We **suggest** the use of narrowband UVB or UVA1 in *children and adolescents* after the assessment of skin type (see background text), but frequent and/or protracted treatment cycles should be avoided.	↑	>95%  (24/25)[1] Expert Consensus
We **suggest** that other phototherapy modalities (balneophototherapy, UVAB, BB-UVB, UVA) are to be considered as a second choice.	↑	100%  (25/25) Expert Consensus
We **suggest** that PUVA therapy is only used, when previous treatment cycles with other phototherapies were ineffective or when approved drug treatments are contraindicated, ineffective or have caused side effects.	↑	100%  (25/25) Expert Consensus
We **suggest** co-treatment with topical emollients during phototherapy.	↑	100%  (25/25) Expert Consensus
We **recommend against** the use of prolonged or repeated treatment cycles and maintenance regimens with all phototherapy modalities.	↓↓	100%  (24/24) Expert Consensus

[1] 1 abstention

We **recommend against** the use of all phototherapy modalities in patients with a history of skin cancer and with an increased risk of skin cancer (including photodamaged skin and those on systemic immunosuppressants (see background text)).	↓↓	100%  (25/25) Expert Consensus

Efficacy of different photo(chemo)therapy modalities in clinical trials

Photo(chemo)therapy can be used in patients with moderate-to-severe AE recalcitrant to topical therapy. Background information on photobiology, UV modalities and practical aspects can be found in Appendix I.

The systematic review of Garritsen et al. investigated the efficacy and safety of treatment with photo(chemo)therapy in AE patients up to 26 October 2012.[1] Only RCTs were included. No meta-analysis could be performed due to methodological heterogeneity. Nineteen studies were included with a total of 905 adult participants (sample size range 9 to 180), treatment duration varying between 10 days and 40 weeks, and with a follow-up up to 1 year (mean 15.3 weeks).

Studies on BB-UVB (4 studies, n=120),[2-5] NB-UVB (6, n=188),[6-11] UVA (3, n=84),[4, 5, 10] UVA1 (9, n=259),[6, 8, 9, 12-17] cold-light UVA1 (1, n=50),[17] UVAB (7, n=200),[2, 5, 14, 15, 17-19] full-spectrum light (1, n=20),[20] PUVA (2, n=29),[7, 16] visible light (1, n=20),[3, 10] and balneophototherapy (1, n=90) were included.[11] Concomitant emollient use was permitted in all the RCTs. Detailed tables including patient and treatment characteristics, study outcomes and GRADE assessment can be found in the paper of Garritsen et al.[1] Below is a summary of the results.

Three studies of low[9] to moderate quality[6, 8] compared medium dose (MD) **UVA1 with NB-UVB**; no significant difference was found in clinical signs (apart from 1 clinical sign instrument (Leicester Sign Score) in favour of NB-UVB in 1 RCT of low-quality[9]).

Three studies of low[15], moderate[14] and high[17] quality found **UVA1** [one medium dose (MD) and two high dose (HD) protocols] to be significantly more effective than **UVAB** regarding clinical signs and symptoms.[14, 15, 17] No significant difference was found between **MD-UVA1** and **HD-UVA1** after stop of treatment and after 6 months of follow-up in two studies of very low[13] (pilot study) and moderate quality (intrapatient, side to side comparison study).[12]

One low-quality study showed more improvement in clinical signs and symptoms of **NB-UVB** versus **UVA and visible light** up to 3 months of follow-up (no statistical significance mentioned).[10]

One low-quality study showed **UVB** to be significantly more effective compared to placebo **visible light** for clinical signs and symptoms.[3]

One study of very low quality[5] and one of low quality[2] showed **UVAB** to be significantly more effective compared to **UVA** (clinical signs) and **BB-UVB** (clinical signs and symptoms) respectively. Another study of low quality showed **UVA** to significantly reduce clinical signs compared to **BB-UVB**.[4] **UVAB** combined **with topical corticosteroids** led to significantly greater reduction in clinical signs and symptoms than UVAB alone in a moderate-quality study.[19] **UVAB** compared to **ciclosporin** was significantly less effective on the short-term for clinical signs and QoL.[18]

PUVA turned out to be significantly more effective than **MD-UVA1** in clinical signs and duration of remission in one low-quality study.[16] Between **PUVA** and **NB-UVB** no significant difference was demonstrated in clinical signs after treatment nor after follow-up up to 1 year in one very low-quality study.[7]

Full-spectrum light (320-5000nm) versus controls with emollients significantly reduced clinical signs up to a follow-up of 4 weeks in one very low-quality study.[20]

Balneophototherapy (saltwater bath plus NB-UVB) was significantly more effective than **NB-UVB** for clinical signs up to 6 months of follow-up in a low-quality study.[11]

Based on this systematic review conclusions must be drawn carefully, because of small and heterogeneous studies, high degrees of bias and varying levels of evidence. In terms of efficacy most evidence is available for MD-UVA-1 and NB-UVB. No difference was found between HD-UVA1 and MD-UVA1; more evidence was available for MD-UVA1. UVAB was more effective than UVA and BB-UVB, but not compared to UVA1. Other options are PUVA, full-spectrum light and balneophototherapy, but studies were small and of low quality. No suitable RCTs on heliothalassotherapy or Goeckerman therapy (coal tar plus UVB) were found.

Of the two RCTs retrieved from the additional search, the first compared **UVA** (n=30) with **UVB** (n=30) thrice weekly for a maximum of 12 weeks, with a follow up of 3 months, in moderate-to-severe AE patients.[21] Both modalities had a similar effect on reduction in clinical signs. The second evaluated **HD-UVA1** (130 J/cm^2) versus **MD-UVA1** (60 J/cm^2) five times weekly for 3 weeks in 27 severe adult AE patients.[22] Patients with skin type III-IV responded significantly more to HD-UVA1 than MD-UVA1 concerning clinical signs; patients with skin type II showed no difference between these two.

No evidence on efficacy of phototherapy in acute versus chronic AE was found, and no RCTs for children were found. Apart from some (mostly retrospective) case series,[23-29] two non-randomized studies have been published. In a comparative non-randomized study, 29 AE children and adolescents, aged 3-16 years, were treated with NB-UVB phototherapy for 12 weeks and compared with 26 patients who chose not to undertake treatment.[30] There was a 61% reduction in mean Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score at week 12 in the NB-UVB cohort compared with an increase of 6% in the unexposed cohort. An open-label trial without control group assessed the effectiveness and safety of NB-UVB phototherapy in 30 AE children, aged 4-14 years. There was a significant reduction in severity at the end of treatment compared to baseline; this effect maintained during 2 years of follow-up.[31]

Concluding this section, we must emphasise that the use of phototherapy for AE is largely empiric and based on relatively few evidence-based data. There is a clear need for further research on the effectiveness and safety of phototherapy in AE, given that it is frequently used in AE patients.[32]

Safety of different photo(chemo)therapy modalities in clinical trials

In the RCTs included in the systematic review of Garritsen[1] and in the additional two RCTs[21, 22] no serious side-effects during the treatment and up to 1 year of follow-up were reported. Short-term side-effects (up to 1 year of follow-up) include xerosis cutis, erythema and burning, pruritus (UVA1 and full-spectrum light), gastrointestinal diseases (balneophototehrapy), exacerbations of AE (UVA, NVB-UVB, visible light, full-spectrum light), folliculitis (UVA1, PUVA), and photo-onycholysis (PUVA). The open-label trial performed in children reported grade II erythema, reactivation of herpes labialis and chickenpox as side-effects. Follow-up up to 2 years did not show any significant side-effects.

However, it is evident that our current knowledge on the safety of phototherapy in patients with AE is poor because there are no data from RCTs or registries enrolling large patients' cohorts and with prolonged follow-up.

These studies are available for patients treated with UVA1,[33] BB-UVB and NB-UVB for other indications, mainly psoriasis, and they did not show increased risks of basal cell carcinoma, squamous cell carcinoma and melanoma.[34, 35] However, due to the lack of adequate prospective studies a follow up of patients who underwent repeated and protracted treatment cycles is recommended, particularly in lighter skin types.[36] The cancerogenic risk of PUVA is well demonstrated in psoriatic patients, and therefore caution is recommended also in AE patients.[36,37, 38] However, extrapolating the magnitude of the risk observed with PUVA in patients with psoriasis to the risk in patients with AE is not always correct because psoriatic patients (historically) may have been treated more often with immunosuppressants and / or mutagenic drug therapies.

In patients who use systemic immunosuppressants, especially cyclosporine and azathioprine, phototherapy is not recommended based on their risk of co-carcinogenicity (see chapter Conventional systemic drugs). There are few papers available on combination therapy and the long-term safety in psoriatic patients;[39, 40] no papers were found specifically for AE. (see separate appendix)

References

[1] Garritsen FM, Brouwer MW, Limpens J, Spuls PI. Photo(chemo)therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. Br J Dermatol. 2014;170; 501-513.
[2] Jekler J, Larko O. Combined UVA-UVB versus UVB phototherapy for atopic dermatitis: a paired-comparison study. Journal of the American Academy of Dermatology. 1990;22; 49-53.
[3] Jekler J, Larko O. UVB phototherapy of atopic dermatitis. Br J Dermatol. 1988;119; 697-705.
[4] Jekler J, Larko O. UVA solarium versus UVB phototherapy of atopic dermatitis: a paired-comparison study. Br J Dermatol. 1991;125; 569-572.
[5] Jekler J, Larko O. Phototherapy for atopic dermatitis with ultraviolet A (UVA), low-dose UVB and combined UVA and UVB: two paired-comparison studies. Photodermatol Photoimmunol Photomed. 1991;8; 151-156.
[6] Majoie IM, Oldhoff JM, van Weelden H, Laaper-Ertmann M, Bousema MT, Sigurdsson V, et al. Narrowband ultraviolet B and medium-dose ultraviolet A1 are equally effective in the treatment of moderate to severe atopic dermatitis. Journal of the American Academy of Dermatology. 2009;60; 77-84.
[7] Der-Petrossian M, Seeber A, Honigsmann H, Tanew A. Half-side comparison study on the efficacy of 8-methoxypsoralen bath-PUVA versus narrow-band ultraviolet B phototherapy in patients with severe chronic atopic dermatitis. Br J Dermatol. 2000;142; 39-43.
[8] Gambichler T, Othlinghaus N, Tomi NS, Holland-Letz T, Boms S, Skrygan M, et al. Medium-dose ultraviolet (UV) A1 vs. narrowband UVB phototherapy in atopic eczema: a randomized crossover study. Br J Dermatol. 2009;160; 652-658.
[9] Legat FJ, Hofer A, Brabek E, Quehenberger F, Kerl H, Wolf P. Narrowband UV-B vs medium-dose UV-A1 phototherapy in chronic atopic dermatitis. Arch Dermatol. 2003;139; 223-224.
[10] Reynolds NJ, Franklin V, Gray JC, Diffey BL, Farr PM. Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. Lancet. 2001;357; 2012-2016.
[11] Heinlin J, Schiffner-Rohe J, Schiffner R, Einsele-Kramer B, Landthaler M, Klein A, et al. A first prospective randomized controlled trial on the efficacy and safety of synchronous balneophototherapy vs. narrow-band UVB monotherapy for atopic dermatitis. J Eur Acad Dermatol Venereol. 2011;25; 765-773.
[12] Tzaneva S, Seeber A, Schwaiger M, Honigsmann H, Tanew A. High-dose versus medium-dose UVA1 phototherapy for patients with severe generalized atopic dermatitis. Journal of the American Academy of Dermatology. 2001;45; 503-507.
[13] Dittmar HC, Pflieger D, Schopf E, Simon JC. [UVA1 phototherapy. Pilot study of dose finding in acute exacerbated atopic dermatitis]. Hautarzt. 2001;52; 423-427.
[14] Krutmann J, Czech W, Diepgen T, Niedner R, Kapp A, Schopf E. High-dose UVA1 therapy in the treatment of patients with atopic dermatitis. Journal of the American Academy of Dermatology. 1992;26; 225-230.
[15] Krutmann J, Diepgen TL, Luger TA, Grabbe S, Meffert H, Sonnichsen N, et al. High-dose UVA1 therapy for atopic dermatitis: results of a multicenter trial. Journal of the American Academy of Dermatology. 1998;38; 589-593.
[16] Tzaneva S, Kittler H, Holzer G, Reljic D, Weber M, Honigsmann H, et al. 5-Methoxypsoralen plus ultraviolet (UV) A is superior to medium-dose UVA1 in the treatment of severe atopic dermatitis: a randomized crossover trial. Br J Dermatol. 2010;162; 655-660.
[17] von Kobyletzki G, Pieck C, Hoffmann K, Freitag M, Altmeyer P. Medium-dose UVA1 cold-light phototherapy in the treatment of severe atopic dermatitis. Journal of the American Academy of Dermatology. 1999;41; 931-937.

[18] Granlund H, Erkko P, Remitz A, Langeland T, Helsing P, Nuutinen M, et al. Comparison of cyclosporin and UVAB phototherapy for intermittent one-year treatment of atopic dermatitis. Acta Derm Venereol. 2001;81; 22-27.
[19] Valkova S, Velkova A. UVA/UVB phototherapy for atopic dermatitis revisited. J Dermatolog Treat. 2004;15; 239-244.
[20] Byun HJ, Lee HI, Kim B, Kim MN, Hong H, Choi Y, et al. Full-spectrum light phototherapy for atopic dermatitis. International journal of dermatology. 2011;50; 94-101.
[21] Qayyum S, Asad F, Agrawal R, Khurshid K, Rani Z, Pal SS. Comparison of efficacy and safety of ultraviolet A radiation versus ultraviolet B radiation in atopic dermatitis. Journal of pakistan association of dermatologists. 2016;26; 223-228.
[22] Pacifico A, Iacovelli P, Damiani G, Ferraro C, Cazzaniga S, Conic RRZ, et al. 'High dose' vs. 'medium dose' UVA1 phototherapy in italian patients with severe atopic dermatitis. J Eur Acad Dermatol Venereol. 2019;33; 718-724.
[23] Collins P, Ferguson J. Narrowband (TL-01) UVB air-conditioned phototherapy for atopic eczema in children. Br J Dermatol. 1995;133; 653-655.
[24] Jury CS, McHenry P, Burden AD, Lever R, Bilsland D. Narrowband ultraviolet B (UVB) phototherapy in children. Clin Exp Dermatol. 2006;31; 196-199.
[25] Clayton TH, Clark SM, Turner D, Goulden V. The treatment of severe atopic dermatitis in childhood with narrowband ultraviolet B phototherapy. Clin Exp Dermatol. 2007;32; 28-33.
[26] Tay YK, Morelli JG, Weston WL. Experience with UVB phototherapy in children. Pediatr Dermatol. 1996;13; 406-409.
[27] Sheehan MP, Atherton DJ, Norris P, Hawk J. Oral psoralen photochemotherapy in severe childhood atopic eczema: an update. Br J Dermatol. 1993;129; 431-436.
[28] Mok ZR, Koh MJ, Chong WS. Is phototherapy useful in the treatment of atopic dermatitis in asian children? A 5-year report from singapore. Pediatr Dermatol. 2014;31; 698-702.
[29] 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; 727-729.
[30] 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; 150-156.
[31] Dayal S, Pathak K, Sahu P, Jain VK. Narrowband UV-B phototherapy in childhood atopic dermatitis: efficacy and safety. An Bras Dermatol. 2017;92; 801-806.
[32] Vermeulen FM, Gerbens LAA, Schmitt J, Deleuran M, Irvine AD, Logan K, et al. The European TREatment of ATopic eczema (TREAT) Registry Taskforce survey: prescribing practices in Europe for phototherapy and systemic therapy in adult patients with moderate-to-severe atopic eczema. Br J Dermatol. 2020.
[33] Bedair K, Elhadad A, Hamad S, Ferguson J, Donnan P, Dawe RS. No association between whole-body ultraviolet A1 phototherapy and skin cancers in humans: a cancer registry linkage study. British Journal of Dermatology. 2020.
[34] Weischer M, Blum A, Eberhard F, Rocken M, Berneburg M. No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband UVB phototherapy: A first retrospective study. Acta Dermato-Venereologica. 2004;84; 370-374.
[35] Lee E, Koo J, Berger T. UVB phototherapy and skin cancer risk: a review of the literature. International journal of dermatology. 2005;44; 355-360.
[36] Archier E, Devaux S, Castela E, Gallini A, Aubin F, Le Maitre M, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. J Eur Acad Dermatol Venereol. 2012;26 Suppl 3; 22-31.
[37] Stern RS, Liebman EJ, Vakeva L. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. J Natl Cancer Inst. 1998;90; 1278-1284.

[38] Stern RS, Nichols KT, Vakeva LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study. N Engl J Med. 1997;336; 1041-1045.
[39] Paul CF, Ho VC, McGeown C, Christophers E, Schmidtmann B, Guillaume JC, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. J Invest Dermatol. 2003;120; 211-216.
[40] Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. Lancet. 2001;358; 1042-1045.