Antimicrobial treatment

We **suggest** treatment with topical antiseptic drugs – including sodium hypochlorite 0.005% baths -in patients with a history of recurrent skin infections.	↑	100%  (24/24) Expert Consensus

Anti-bacterial treatment

We **recommend** a short course of systemic antibiotics only in AE patients with extensive clinically superinfected lesions.	↑↑	100%  (25/25) Expert Consensus
We **suggest** against the long-term application of topical antibiotics, due to the risk of resistance development .	↓	
We **suggest** that topical anti-inflammatory treatments are continued during the treatment of Staphylococcus aureus superinfection episodes.	↑	

The prevalence of *Staphylococcus aureus* (SA) colonization among patients with AE is typically above 80% for lesional skin and 40% for nonlesional skin versus 10% in healthy individuals, but this depends largely on the culture methods used. The density of the colonization correlates with the disease severity.[1] Topical corticosteroids and calcineurin inhibitors reduce the colonization rate of SA in AE. Although AE patients are prone to SA skin infections, most AE patients colonized by SA do not show overt signs of infection (i.e. weeping, honey-coloured crusts, and pustules). Clinical signs of skin inflammation during AE flares may overlap with signs of skin infection, making the diagnosis of skin infection *per se* challenging.[2] Bacterial swabs are commonly unhelpful, as they do not alter the treatment approach, unless the patient is infected with a resistant bacterial species. SA is a major trigger of AE flares, but its role in the development of AE is still debated. There are a number of mechanisms through which SA can drive eczematous inflammation, including the release of superantigen toxins, which enhance T cell activation of superantigen-specific and allergen-specific T cells, the expression of IgE anti-staphylococcal antibodies and increased expression of IL-31 which leads to pruritus and subsequent scratching.[2, 3] Scratching favors binding of *SA* to the skin, and the increased amount of *SA* derived ceramidase aggravates the skin barrier defect. Moreover, superantigen production increases expression of alternative glucocorticoid receptors that do not bind to topical corticosteroids, which leads to treatment resistance.[4] Biofilm formation by AE-associated staphylococci most certainly also plays a major role in the occlusion of sweat ducts and leads to inflammation and pruritus.[4]

A Cochrane review by George et al.[5] with 41 studies and 1,753 participants assessed the effect of different interventions to reduce SA on the skin in people with AE. Four studies evaluated oral antibiotics versus placebo. No difference was found in the global severity assessment (RR 0.80; 95% CI 0.18 to 3.50; 2 RCTs; GRADE: low-quality) and little to no effect was reported for QoL (MD 0.11, 95% CI -0.10 to 0.32; 1 RCT; GRADE moderate-quality). Fourteen studies compared topical corticosteroids plus antibiotic with topical corticosteroids alone. Steroids/antibiotics combination participant may have a slightly greater improvement in the global signs and symptoms (RR 1.10, 95% CI 1.00 to 1.21; 3 RCTs; GRADE: low-quality). For QoL, little to no effect was found (MD -0.18, 95% CI -0.40 to 0.04; 1 RCT GRADE: moderate-quality). For bleach baths versus placebo or bath emollients, no difference was reported in the global improvement at one month follow-up (RR 0.78; 95% CI 0.37 to 1.63; 1 RCT; GRADE: low-quality) and little to no effect was documented for QoL (MD 0.90; 95% CI -1.32 to 3.12; 1 RCT; GRADE: moderate quality). This corresponds to recent data showing no antimicrobial effect in vitro of diluted bleach baths.[6]

For all three interventions adverse events leading to withdrawal of treatment were rare and evidence was very low quality. For antibiotic resistance, no significant difference was demonstrated between intervention groups and placebo but results remain uncertain because quality of evidence was very low.

Eight randomized controlled trials evaluated treated textiles (as silver) versus placebo, studies were not pooled due to heterogeneous design but no clear advantage was reported. Juenger et al.[7] found no effect in the overall disease control of AE in the silver textile group compared with non-silver textile (RR 2.40; 95% CI 0.91 to 6.36; RoB: high) and Gauger et al.[8] reported no significant difference between groups in the quality of life questionnaire (RoB: high). For summary of findings tables (modified), see appendix III.

Anti-viral treatment

We **recommend** to treat eczema herpeticum without delay using systemic antiviral therapy, such as aciclovir.	↑↑	100%  (25/25) Expert Consensus
We **recommend** to perform vaccinations in line with national guidelines.	↑↑	

Viral infections including herpes simplex, varicella zoster, molluscum contagiosum, smallpox and coxsackie viruses occur more frequently in AE patients than in healthy individuals, with a tendency to disseminated, widespread disease.[9]

Eczema herpeticum (EH), a disseminated herpes simplex virus (HSV) infection, is a potentially serious complication of AE that requires immediate medical action. Patients, mostly children, present with disseminated vesicles, fever and lymphadenopathy and can develop complications such as keratoconjunctivitis, meningitis and encephalitis. Predisposing factors of first episode of EH or recurrent EH are early onset and severe or untreated forms of AE with high IgE levels and atopic comorbidities (extrinsic AE). Pre-treatment with topical corticosteroids or calcineurin inhibitors is not associated with an increased risk of developing EH. There is no evidence to recommend discontinuation of topical anti-inflammatory treatments during an EH outbreak.[10] Mainstay of EH therapy is systemic treatment with aciclovir or valaciclovir.[11] Treatment should be started immediately, once the clinical diagnosis is made.[12]

Varicella-zoster virus (VZV) infection in an immunocompetent child is usually a mild, self-limiting disease. This infection is, however, known to facilitate secondary local or systemic bacterial infection and a particular concern in children with AE. Earlier studies demonstrated the safety and efficacy of VZV vaccination in these children who appear to benefit from this vaccination.[13] Moreover, in children with AE, immune response to VZV vaccine is comparable to healthy children.[14] Therefore, parents of atopic children should be encouraged to fully immunize their children depending on specific local guidelines.

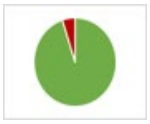
Molluscum contagiosum virus (MCV) infection is in general benign and self-limiting but frequent in patients with severe AE. A large variety of topical treatments have been reported such as cantharidin, potassium hydroxide, tretinoin cream, and topical cidofovir.[15] Physical therapies including cryotherapy and curettage are also effective, but not always well tolerated in paediatric patients and usually unnecessary given the self-limiting nature of MCV infections.[16] Topical treatment of AE with TCS should be continued during MCV infection.

Eczema vaccinatum (EV) is a complication of smallpox vaccination known to occur in AE patients. The vaccinia virus disseminates and causes an extensive rash and severe systemic illness with a mortality rate estimate at 5-40%.[17] Therefore, smallpox vaccination is contraindicated in patients with a history of or currently active AE.[18] The existence of an attenuated vaccine (Modified Vaccinia Ankara virus) and three antiviral drugs, in addition to vaccinia immunoglobulin, provides means of preventing or treating EV.[19, 20] Should a smallpox outbreak necessitate an emergency mass vaccination, the choice of vaccination strategies, such as ring or mass vaccination, has to be determined by policymakers.

Eczema coxsackium (EC) is a disseminated form of coxsackie virus infection mostly occurring in children with active AE lesions.[21] The coxsackie virus A6 strain leads to atypical disease manifestations, which are classified as i) a diffuse form (lesions extended to the trunk), ii) an acral form (lesions with a mainly acral distribution), or iii) eczema coxsackium (disseminated lesions on preexisting eczematous areas).[22] This rash may be confused with bullous impetigo or eczema herpeticum. Symptomatic treatment includes use of topical corticosteroids and wet wrap therapy.[23, 24]

Regional vaccination programmes should be followed by all AE patients as recommended. The denial of vaccination because of diagnosed AE is a misconception possibly leading to fatal consequences.

Anti-fungal treatment

We **suggest** topical or systemic antifungal therapy in some patients with AE, mainly in those suffering from the "head and neck" variant of AE. and with demonstrated IgE-sensitization to *Malassezia spp*.	↑	>95%  (23/24) Expert Consensus

Despite its role as a commensal on healthy human skin, Malassezia spp. is attributed a pathogenic role in AE, as it may interact with the local skin immune response and barrier function. Through a deficient skin barrier, Malassezia spp may activate keratinocytes and dendritic cells causing secretion of a range of pro-inflammatory cytokines including IL-4, IL-13 and-IL 17.[25-27] Several randomized, placebo controlled trials investigated the benefit of topical or systemic antifungal treatment for AE patients.[28-30] The ambiguous results of these clinical trials might be attributed to selection bias. It can be speculated that antifungal therapies are more effective in certain subgroup of AE. It seems for example that antifungal therapy shows beneficial effects in patients with a head-neck-type distributed AE and detectable IgE-mediated sensitization against Malassezia.[31] It has also been shown that sensitization against this skin-colonizing yeast can correlate with disease activity.[32] The most common class of antifungal drugs prescribed for AE patients are azoles such as ketoconazole and itraconazole which have also some anti-inflammatory properties.[29] Due to a better benefit:side effect ratio imidazole derivates (fluconazole or itraconazole) should be prescribed instead of ketoconazole for systemic treatment. In summary, antifungal treatment with either topical ketoconazole or ciclopiroxolamine or systemic itraconazole or fluconazole can be considered for those patients who suffer from head–neck dermatitis, particularly for those who are characterized by clear IgE-sensitization to Malassezia spp.

References

[1] Totté JE, van der Feltz WT, Hennekam M, van Belkum A, van Zuuren EJ, Pasmans SG. Prevalence and odds of Staphylococcus aureus carriage in atopic dermatitis: a systematic review and meta-analysis. Br J Dermatol. 2016;175; 687-695.
[2] Alexander H, Paller AS, Traidl-Hoffmann C, Beck LA, De Benedetto A, Dhar S, et al. The role of bacterial skin infections in atopic dermatitis: expert statement and review from the International Eczema Council Skin Infection Group. Br J Dermatol. 2020;182; 1331-1342.
[3] Cornelissen C, Marquardt Y, Czaja K, Wenzel J, Frank J, Luscher-Firzlaff J, et al. IL-31 regulates differentiation and filaggrin expression in human organotypic skin models. J Allergy Clin Immunol. 2012;129; 426-433, 433.e421-428.
[4] Schlievert PM, Case LC, Strandberg KL, Abrams BB, Leung DYM. Superantigen profile of Staphylococcus aureus isolates from patients with steroid-resistant atopic dermatitis. Clin Infect Dis. 2008;46; 1562-1567.
[5] George SM, Karanovic S, Harrison DA, Rani A, Birnie AJ, Bath-Hextall FJ, et al. Interventions to reduce Staphylococcus aureus in the management of eczema. Cochrane Database Syst Rev. 2019;2019.
[6] Sawada Y, Tong Y, Barangi M, Hata T, Williams MR, Nakatsuji T, et al. Dilute bleach baths used for treatment of atopic dermatitis are not antimicrobial in vitro. J Allergy Clin Immunol. 2019;143; 1946-1948.
[7] Juenger M, Ladwig A, Staecker S, Arnold A, Kramer A, Daeschlein G, et al. Efficacy and safety of silver textile in the treatment of atopic dermatitis (AD). Curr Med Res Opin. 2006;22; 739-750.
[8] Gauger A, Fischer S, Mempel M, Schaefer T, Foelster-Holst R, Abeck D, et al. Efficacy and functionality of silver-coated textiles in patients with atopic eczema. J Eur Acad Dermatol Venereol. 2006;20; 534-541.
[9] Wollenberg A, Zoch C, Wetzel S, Plewig G, Przybilla B. Predisposing factors and clinical features of eczema herpeticum: a retrospective analysis of 100 cases. Journal of the American Academy of Dermatology. 2003;49; 198-205.
[10] Seegräber M, Worm M, Werfel T, Svensson A, Novak N, Simon D, et al. Recurrent eczema herpeticum - a retrospective European multicenter study evaluating the clinical characteristics of eczema herpeticum cases in atopic dermatitis patients. J Eur Acad Dermatol Venereol. 2020;34; 1074-1079.
[11] Ong PY, Leung DY. Bacterial and Viral Infections in Atopic Dermatitis: a Comprehensive Review. Clin Rev Allergy Immunol. 2016;51; 329-337.
[12] Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018;32; 657-682.
[13] Kreth HW, Hoeger PH. Safety, reactogenicity, and immunogenicity of live attenuated varicella vaccine in children between 1 and 9 years of age with atopic dermatitis. Eur J Pediatr. 2006;165; 677-683.
[14] Schneider L, Weinberg A, Boguniewicz M, Taylor P, Oettgen H, Heughan L, et al. Immune response to varicella vaccine in children with atopic dermatitis compared with nonatopic controls. The Journal of allergy and clinical immunology. 2010;126; 1306-1307.e1302.
[15] Osier E, Eichenfield L. The Utility of Cantharidin for the Treatment of Molluscum Contagiosum. Pediatric dermatology. 2015;32.
[16] Wollenberg A, Wetzel S, Burgdorf WH, Haas J. Viral infections in atopic dermatitis: pathogenic aspects and clinical management. J Allergy Clin Immunol. 2003;112; 667-674.
[17] Rush J, Dinulos JG. Childhood skin and soft tissue infections: new discoveries and guidelines regarding the management of bacterial soft tissue infections, molluscum contagiosum, and warts. Curr Opin Pediatr. 2016;28; 250-257.

[18] Wollenberg A, Engler R. Smallpox, vaccination and adverse reactions to smallpox vaccine. Curr Opin Allergy Clin Immunol. 2004;4; 271-275.
[19] Reed JL, Scott DE, Bray M. Eczema vaccinatum. Clin Infect Dis. 2012;54; 832-840.
[20] Darsow U, Sbornik M, Rombold S, Katzer K, von Sonnenburg F, Behrendt H, et al. Long-term safety of replication-defective smallpox vaccine (MVA-BN) in atopic eczema and allergic rhinitis. J Eur Acad Dermatol Venereol. 2016;30; 1971-1977.
[21] Mathes EF, Oza V, Frieden IJ, Cordoro KM, Yagi S, Howard R, et al. "Eczema coxsackium" and unusual cutaneous findings in an enterovirus outbreak. Pediatrics. 2013;132; e149-157.
[22] Neri I, Dondi A, Wollenberg A, Ricci L, Ricci G, Piccirilli G, et al. Atypical Forms of Hand, Foot, and Mouth Disease: A Prospective Study of 47 Italian Children. Pediatr Dermatol. 2016;33; 429-437.
[23] Lynch MD, Sears A, Cookson H, Lew T, Laftah Z, Orrin L, et al. Disseminated coxsackievirus A6 affecting children with atopic dermatitis. Clinical and Experimental Dermatology. 2015;40; 525-528.
[24] Johnson VK, Hayman JL, McCarthy CA, Cardona ID. Successful treatment of eczema coxsackium with wet wrap therapy and low-dose topical corticosteroid. J Allergy Clin Immunol Pract. 2014;2; 803-804.
[25] Sparber F, De Gregorio C, Steckholzer S, Ferreira FM, Dolowschiak T, Ruchti F, et al. The Skin Commensal Yeast Malassezia Triggers a Type 17 Response that Coordinates Anti-fungal Immunity and Exacerbates Skin Inflammation. Cell Host Microbe. 2019;25; 389-403.e386.
[26] Thammahong A, Kiatsurayanon C, Edwards SW, Rerknimitr P, Chiewchengchol D. The clinical significance of fungi in atopic dermatitis. International journal of dermatology. 2020;59; 926-935.
[27] Glatz M, Bosshard PP, Hoetzenecker W, Schmid-Grendelmeier P. The Role of Malassezia spp. in Atopic Dermatitis. J Clin Med. 2015;4; 1217-1228.
[28] Kaffenberger BH, Mathis J, Zirwas MJ. A retrospective descriptive study of oral azole antifungal agents in patients with patch test-negative head and neck predominant atopic dermatitis. Journal of the American Academy of Dermatology. 2014;71; 480-483.
[29] Svejgaard E, Larsen PO, Deleuran M, Ternowitz T, Roed-Petersen J, Nilsson J. Treatment of head and neck dermatitis comparing itraconazole 200 mg and 400 mg daily for 1 week with placebo. J Eur Acad Dermatol Venereol. 2004;18; 445-449.
[30] Lorette G, Ermosilla V. Clinical efficacy of a new ciclopiroxolamine/zinc pyrithione shampoo in scalp seborrheic dermatitis treatment. Eur J Dermatol. 2006;16; 558-564.
[31] Brodská P, Panzner P, Pizinger K, Schmid-Grendelmeier P. IgE-Mediated Sensitization to Malassezia in Atopic Dermatitis: More Common in Male Patients and in Head and Neck Type. Dermatitis. 2014;25; 120-126.
[32] Glatz M, Buchner M, Von Bartenwerffer W, Schmid-Grendelmeier P, Worm M, Hedderich J, et al. Malassezia spp.-specific immunoglobulin E level is a marker for severity of atopic dermatitis in adults. Acta dermato-venereologica. 2015;95; 191-196.