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REVIEW ARTICLE

Infections in Patients with Atopic Dermatitis and the Influence of Treatment

Maddalena Napolitano[1] · Maria Esposito[2,3] · Maria Concetta Fargnoli[4] · Giampiero Girolomoni[5] · Paolo Romita[6] · Elena Nicoli[7] · Paolo Matruglio[7] · Caterina Foti[6]

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Abstract

Atopic dermatitis (AD) is a T helper 2-mediated chronic inflammatory skin disease that affects children and adults. Patients with AD are prone to recurrent infections of the skin and other organs, which can severely worsen the disease course. This review summarises the current evidence on the aetiology, pathogenesis, treatment and prevention of infections in patients with AD. PubMed was searched for English-language research articles, systematic reviews, meta-analyses and guidelines published until February 2023 using the key term "atopic dermatitis" and terms relevant to infections. Patients with AD have an increased risk of bacterial, viral and fungal infections of the skin, mainly due to impaired barrier function, altered immune response and frequent scratching. The most common pathogens are *Staphylococcus aureus* and herpes simplex virus, which can cause impetigo, folliculitis, abscesses, eczema herpeticum and other complications. They also appear to increase susceptibility to systemic infections, including respiratory and urinary tract infections and sepsis. Certain systemic treatments for AD, such as mycophenolate mofetil and Janus kinase inhibitors, increase the risk of viral infections. Prevention and treatment of recurrent infections in patients with AD require a multifaceted approach that includes topical and systemic antimicrobials, skin care and effective control of AD symptoms (to break the itch–scratch cycle). Preventing and limiting the development of infections are important considerations in choosing an AD treatment.

Key Points

Patients with atopic dermatitis (AD) are prone to recurrent bacterial, fungal and viral skin infections that can have negative consequences on the disease course.

Recurrent infections are most commonly caused by *Staphylococcus aureus* and herpes simplex virus; these can also lead to infections of other organ systems including the lungs and the urinary tract.

Prevention and treatment of infections in patients with AD may require topical and systemic antimicrobials, appropriate skin care and effective control of AD signs and symptoms.

1 Introduction

Atopic dermatitis (AD) is a common, chronic relapsing and remitting type 2 inflammatory skin disease, which has severe physical and psychological effects and greatly

Maddalena Napolitano, Maria Esposito have contributed equally to this work.

✉ Maria Concetta Fargnoli
mariaconcetta.fargnoli@ifo.it

1 Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

2 Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Via Vetoio, Coppito 2, 67100 L'Aquila, Italy

3 UOSD General and Oncological Dermatology, Ospedale San Salvatore, L'Aquila, Italy

4 San Gallicano Dermatological Institute - IRCCS, Rome, Italy

5 Department of Medicine, Section of Dermatology, University of Verona, Verona, Italy

6 Department of Precision Medicine and Regeneration and Ionian Area, Unit of Dermatology, University of Bari Aldo Moro, Bari, Italy

7 Sanofi, Milan, Italy

reduces individuals' quality of life [1–5]. In the acute phase, AD lesions usually appear as erythematous patches with exudation, blistering and crusting, while chronic phase lesions are characterised by scaling, fissuring (cracking) and lichenification (thickening) [1]. AD may be associated with severe itch, which can lead to sleep disturbances and added physiological distress, with downstream effects on work/academic performance and social functioning [6, 7].

Although AD is traditionally considered a childhood disease that remits before adulthood, it is now understood that AD can affect adults, either as an adulthood-onset condition or as childhood-persistent or relapsed AD [8], with an increased prevalence among older adults (aged > 65 years) [9, 10]. The distribution of AD lesions is age specific [8, 11]. In infants, erythematous papules, patches or plaques are usually located on the face (specifically the cheeks), scalp, trunk and extremities, while older children mostly have patches on flexural surfaces, and adults develop dry, scaly patches on their head/neck, trunk and extremities.

AD may predispose patients to recurrent cutaneous and extra-cutaneous infections, which cause significant morbidity and increase the risk of developing systemic infections if left untreated [12, 13]. In all age groups, AD increases the risk of emergency department visits for bacterial, viral or fungal skin infections [14]. Consequently, the burden of AD and its sequelae on the healthcare system must be considerable [15]. In this narrative review, we will summarise the pathophysiology of AD, the types and causes of skin and extracutaneous infections and the management of AD and related infections.

2 Methods

A literature search of PubMed was undertaken on 24 February 2023 to identify English-language papers published in indexed journals in the last 20 years according to the following research key words: (atopic dermatitis) AND (infections OR infection OR infestations OR infestation) AND (recurrent OR recurring OR repeat OR persistent OR regular OR chronic OR long-term OR long term); infections in atopic dermatitis. After removing duplicate articles, potentially relevant papers were chosen on the basis of the title and abstract. The search results were supplemented with additional literature identified on an ad hoc basis or via the bibliographies of identified studies.

3 Aetiological and Pathogenic Factors Impacting Infection Risk

AD is a multifactorial disease that arises from a complex interplay between genetic factors, type-2–skewed immune dysregulation, skin barrier defects and environmental triggers [12, 16]. A family history of atopic diseases, especially AD, is the most significant risk factor for AD, which is thought to be triggered by environmental or endogenous factors in genetically susceptible individuals [1, 17].

Individuals with loss-of-function (LOF) mutations in the *FLG* gene (encoding the epidermal protein filaggrin) are more predisposed to developing AD than those without [1, 18]. Low filaggrin levels can cause decreased skin hydration and increased skin permeability to environmental insults, triggering a hyperimmune response. Indeed, Singaporean Chinese patients with AD and LOF *FLG* mutations have a seven-fold higher risk of experiencing ≥ 4 skin infections requiring antibiotics within 1 year compared with those with no mutations [19].

Other loci of interest include the T helper 2 (Th2) cytokine cluster on chromosome 5q31.1 and a locus on chromosome 11q13.5 [20]. Genetic variations in the Th2 cluster cause epigenetic mechanisms to skew adaptive immune response patterns towards a type-2 phenotype; in this state, common allergens can lead to atopic diseases, for example, food allergies, allergic rhinitis and asthma [1, 4]. The signs and symptoms of AD are caused by functional changes in the epidermis, facilitated by an elevated Th2 immune response [13]. Interleukin (IL)-4, IL-13 and IL-22 suppress filaggrin expression and contribute to immune suppression-mediated changes in barrier function [13]. In the epidermis, these changes include reduced water retention, increased pH, skin sensitisation, permeability to low molecular weight chemicals and susceptibility to infections [1]. Barrier defects in AD are also caused by a lack of essential components in the stratum corneum, such as involucrin, loricrin and claudins, as well as lipid molecules such as ceramide, cholesterol and fatty acids [12].

Pruritus, a key symptom of AD, contributes to pathogenesis by allowing allergens and irritants to permeate the skin, triggering alarm signals that perpetuate the itch–scratch cycle [21, 22]. Pruritus is induced by a complex variety of pruritogens, the most well studied being histamine, which is released from mast cells in the skin in response to immunoglobulin E (IgE) antibodies [23]. However, in AD, other pruritogens, such as endothelin 1, IL-25, IL-33 and thymic stromal lymphopoietin, may play a more important role

in the induction of itch than histamine [1]. Trauma from scratching increases the risk of localised skin infection [24].

Elevated skin pH in patients with AD allows for easier microbial colonisation [25], and the presence of microbial proteases in AD lesions facilitates disruption of the skin barrier [26]. There is also a decrease in the levels of endogenously produced antimicrobial peptides (AMPs), such as cathelicidins and β-defensins, due to the suppressive effect of Th2 cytokines [27]. A decrease in IL-17, which induces AMPs in keratinocytes, may also contribute to the decreased expression of AMPs in AD [28]. Furthermore, a reduced expression of the AMP dermcidin in the sweat of patients with AD may also be another factor responsible for patients' high susceptibility to skin infections [29].

Immune dysregulation can also increase the risk of skin infections in those with AD. For example, functional impairment of polymorphonuclear granulocytes reduces phagocytic activity and intracellular microbial killing [30]. In addition, topical or systemic immunosuppressants used for AD treatment may further reduce host immune response [25].

4 Recurrent Skin Infections

Patients with AD can develop recurrent skin infections caused by bacteria (predominantly *Staphylococcus aureus* and β-haemolytic *Streptococcus pyogenes),* viruses (most often herpes simplex virus [HSV]) and fungi (dermatophytes, *Malassezia* spp. and *Candida* spp.; Table 1) [24, 27, 31].

Table 1 Common types of skin infections (and their causative pathogens) in patients with atopic dermatitis [13, 24]

Type of infection	Common pathogens
Bacterial infections	
Skin and soft tissue infections, including impetigo, cellulitis, skin abscess	*Staphylococcus aureus*, including MRSA; *Streptococcus pyogenes*
Viral infections	
Eczema herpeticum	HSV-1
Eczema coxsackium	Coxsackie virus (often CVA6)
Eczema vaccinatum (rare)	Vaccinia virus in smallpox vaccines
Molluscum contagiosum	Molluscipoxvirus
Fungal infections	
Fungal skin infections	Yeasts (*Malassezia* spp., *Candida* spp.); dermatophytes

HSV herpes simplex virus, *MRSA* methicillin-resistant *Staphylococcus aureus*, *spp* species

4.1 Bacterial Infections

Bacterial infections are the most common type of skin infection seen in patients with AD, and the risk of these infections increases with worsening itch severity, both in patients with a history of other atopic diseases (asthma, allergic rhinitis or conjunctivitis) and in those with lesions in areas that are more susceptible to skin barrier damage, for example, the cubital fossa, popliteal fossa, ears, back and shoulders, armpits, feet and pudendum [32]. Bacterial infections can be difficult to diagnose because infections may have similar symptoms to AD itself or they may be associated with concomitant AD flares, the features of which (erythema, oedema, papulation, oozing and excoriation) can mask signs of infection [24]. Diagnosis may be complicated by the presence of common causative bacteria in non-lesional skin, which limits the usefulness of bacterial cultures in identifying the causative organism.

Staphylococcus aureus is the most frequently isolated bacterial pathogen [33] and commonly causes skin and soft tissue infections (SSTIs) such as impetigo, folliculitis, cellulitis and skin abscesses [13, 24]. *S. pyogenes* is the second most frequent cause of skin infections in AD lesions [13]. This bacterium can cause invasive infections on its own or in conjunction with *S. aureus*. Streptococcal infection presents as well-defined, bright red erythema, thick-walled pustules and heavy crusting [24].

The mechanisms underlying bacterial infection in AD involve bacterial factors such as toxins/virulence factors, enzymes and bacterial cell wall components [27, 34], which cause skin inflammation, epithelial penetration and infection and contribute to bacterial persistence [24].

The best studied bacterial virulence factors are staphylococcal enterotoxins (SEs), also known as superantigens, which induce robust T-cell-mediated inflammation (and the release of proinflammatory cytokines) in AD lesions by binding directly to α/β T-cell receptors [35, 36]. Staphylococcal superantigens also induce the production of IgE antibodies by the host, leading to the release of histamines by basophils [12, 27]. Unlike conventional antigens, superantigens do not require presentation by antigen-presenting cells [36]. Classical staphylococcal superantigens include SEA, SEB, SEC, SED and toxic shock syndrome toxin-1, and non-classical staphylococcal superantigens include SEE and SEG to SEQ [12].

Other staphylococcal toxins/virulence factors include α-toxin, which causes keratinocyte cytotoxicity and lymphocyte apoptosis via signal transduction and activation of transcription 6 (STAT6) [37], and δ-toxin, which increases mast cell degranulation by increasing IgE production [38]. The staphylococcal golden carotenoid pigment prevents the host's neutrophils from producing reactive oxygen species [27].

The pathogenicity of *S. aureus* also depends on the cell wall components, such as staphylococcal protein A, which increases inflammation via signalling through tumour necrosis factor receptor 1 [39] and lipoteichoic acid, which acts via signalling through toll-like receptor 2 and platelet-activating factor receptor [40]. Other cell wall components include peptidoglycan, bacterial capsule polysaccharide and clumping factors (ClfA and ClfB) [27].

Significantly increased colonies of other *Staphylococcus* species, such as *S. epidermidis* and *S. haemolyticus,* are also found in AD lesions [41]. *S. epidermidis* produces AMPs to fight against other bacteria and stimulates keratinocytes to produce more AMPs [42]. An increase in *S. epidermidis* during AD flares represents the body's attempt to control *S. aureus*, indicating that exposure to non-pathogenic strains induces immune tolerance and alleviates AD [43].

AD constitutes a risk factor for the colonisation and transmission of methicillin-resistant *S. aureus* (MRSA); patients with AD have ten-fold higher rates of MRSA colonisation compared with the general population [12]. MRSA is mostly transmitted through close contact with other family members, especially in children, but it can also be transmitted through shared items such as soap, towels, toilet handles, doorknobs, kitchen sinks or even household pets [44]. Compared with methicillin-sensitive *S. aureus* (MSSA), MRSA produces more superantigens and causes significantly more SSTI infections [12, 44].

4.2 Viral Infections

Recurrent viral infections are also prevalent in AD lesions but are relatively less common than bacterial infections [41]. Common causative viruses include HSV, varicella zoster virus, cytomegalovirus and Epstein–Barr virus [45]. Patients with AD may be predisposed to viral skin infections due to genetic variations in selected innate immune response molecules including thymic stromal lymphopoietin, interferon (IFN) α, β, γ and ω and IFN regulatory factor 2 [12, 41, 46]. Activation of the *STAT6* gene also increases viral replication in patients with AD [47].

One of the most common viral infections in patients with AD is HSV infection, which causes eczema herpeticum, mostly as a simultaneous occurrence with *S. aureus* infection [48]. Eczema herpeticum mostly arises in AD lesions on the face, neck, upper trunk and antecubital/popliteal areas, and is often accompanied by fever, malaise, lymphadenopathy, keratoconjunctivitis and potentially encephalitis and septic shock, which can be fatal [49, 50]. Risk factors include moderate-to-severe AD, early onset AD, presence of *FLG* LOF mutations, a history of *S. aureus* skin infection, presence of other allergic diseases, greater allergen sensitisation (i.e. high total serum IgE or peripheral eosinophils) and a Th2 immune response [48–50]. Mechanisms of eczema herpeticum development involve downregulation of IFN-γ and receptors for IFN-α, β, γ and ω, and *S. aureus* α-toxin-induced replication of HSV [46].

Molluscum contagiosum is a common skin condition caused by a poxvirus belonging to the Molluscipoxvirus subfamily [51]. In patients with AD, molluscum contagiosum can spread either in a diffuse manner or along the AD distribution. Less common viral infections of the skin include eczema coxsackium and eczema vaccinatum (Table 1).

4.3 Fungal Infections

Fungal infections are also common in patients with AD, especially those caused by the commensal yeast *Malassezia* [24]. *Malassezia* colonisation drives inflammation particularly in patients with seborrheic dermatitis on their head, neck, upper chest and back [24, 41, 52]. Repeated exposure to *Malassezia* antigens induces autoreactivity to human proteins via molecular mimicry, leading to sustained skin inflammation [53, 54]. In a Japanese study, increased age and AD severity were associated with a higher prevalence and degree of IgE sensitisation to *Malassezia* antigens; *Malassezia*-specific IgE levels were higher in adults with AD compared with children [55].

Candida species, particularly *C. albicans*, are important fungal colonisers in AD [41]. They mostly colonise the skin and mucosal surfaces of the body, such as the genitourinary tract, oral cavity and gastrointestinal tract, causing vulvovaginitis, oral thrush and skin and diaper rash. *Candida* spp. infections can also lead to serious illnesses in individuals with a compromised immune system. *C. albicans* colonisation of the gastrointestinal tract results in antigen sensitisation, which may potentially lead to chronic AD [52]. Moreover, abnormalities in the production of antibodies against *C. albicans* may have a role in AD pathogenesis [56].

5 Extracutaneous and Systemic Infections

In addition to recurrent skin infections, patients with AD are at a greater risk of developing extracutaneous and systemic infections [33, 57]. Although not well understood, the possible risk factors for extracutaneous and systemic infections include a defective skin barrier, dysregulation of innate and adaptive immunity, reduced AMP production, systemic atopy, increased bacterial colonisation/infection of the skin and use of systemic immunosuppressive agents [31, 33].

Children with AD are more prone to infections requiring hospitalisation than those without, particularly respiratory tract and gastrointestinal infections [31, 58, 59]. In a study of Polish children, those with AD had significantly more

episodes of diarrhoea and/or vomiting compared with those without AD (57.8% versus 37.5%; $p < 0.01$) [58]. *S. aureus* was the most common pathogen in stool cultures (19.8% versus 6.6%; $p < 0.01$), followed by strains of *Candida* spp. (9.5% versus 3.7%) [58]. Similarly, in a Danish retrospective cohort study, the risk of upper and lower respiratory tract, gastrointestinal, urinary tract and musculoskeletal infections was 1.2–1.8 times higher in children with AD than in those without [31].

Adult patients with AD also have an increased risk of developing systemic infections, including infections of the upper and lower respiratory tract and lungs, heart, brain, bones and gastrointestinal tract [25, 60]. In a US population-based study, 42.1% of adult patients with AD developed serious infections requiring hospitalisation versus 25.4% of patients without AD [60]. Compared with patients with AD who did not have a serious infection, patients with AD and serious infections experienced higher rates of inpatient mortality due to septicaemia, empyema, pneumonia, abscesses of the lungs and mediastinum, mycobacterial infection, endocarditis, peritonitis and intestinal abscesses, *Clostridium difficile* infection, enterocolitis, encephalitis, MRSA and MSSA [60].

A pooled meta-analysis showed that children and adults with AD are more likely to develop ear infections (26.6% versus 21.9%), streptococcal pharyngitis (8.4% versus 3.1%) and urinary tract infections (8.4% versus 3.1%) compared with those without AD [33].

6 Treatment of Atopic Dermatitis

The goals of AD treatment are to reduce pruritus and skin inflammation, restore barrier function, prevent infection and establish long-term disease control [18]. Currently, there is no cure for AD, but the increasing number of advanced therapies hold promise for achieving long-term disease control [18].

In addition to patient education, use of emollients and allergen avoidance, treatment for AD in adolescents and adults may include topical therapies (including topical corticosteroids [TCS] or calcineurin inhibitors [TCI]), phototherapy and systemic therapies, such as oral corticosteroids and other immunosuppressants (e.g. cyclosporine [CsA], azathioprine [AZT] and methotrexate [MTX]), biological therapies and Janus kinase (JAK) inhibitors to control signs and symptoms [9]. Systemic therapies for AD either modulate the immune system (as is the case for biologic therapies) or suppress the immune system (as is the case for systemic immunosuppressants and oral JAK inhibitors), thus raising the possibility that they may affect a patient's response to infections [61].

6.1 Effect of Systemic Therapies on Infections

6.1.1 Oral Corticosteroids

There are limited data on the incidence of infections during oral corticosteroid therapy in patients with AD [62]. However, data in patients with rheumatologic conditions show a dose-related increase in the risk of serious and opportunistic infections during treatment with these agents [63, 64]. Therefore, oral corticosteroids should be limited to short-term courses for severe flare-ups [62, 65].

6.1.2 Systemic Immunosuppressants

Systemic immunosuppressants (e.g. CsA, MTX, AZT and mycophenolate mofetil [MMF]) are usually administered after the failure of topical treatments and ultraviolet phototherapy [16, 18].

Orally administered CsA, a calcineurin inhibitor, provided symptomatic relief in a study of 11 children with severe AD and decreased commensal *S. aureus* density on lesional skin in patients without an overt skin infection, but had no effect on *S. aureus* density in those with *S.-aureus*-infected AD lesions [36]. The decrease in bacterial density in those without infection was likely due to the improved skin barrier function and healing of lesions induced by CsA. A case–control study comparing real-world patients with AD who were taking CsA with those who were not found no increased risk of infections in the CsA group, with similar rates of eczema herpeticum (the most common infection) in both groups [66]. However, CsA use may increase the risk of MRSA infection in children, according to data from a Brazilian study [67].

There are limited data on the effects of the off-label use of MTX, AZT or MMF for infections in patients with AD. In a case series of children with AD, 16/28 children developed cutaneous infections (usually cellulitis or folliculitis) during treatment with systemic AZT; the average rate of infection across all patients receiving AZT was 0.08 per month [68]. A systematic review of randomised controlled trials (RCTs), cohort studies and case reports of MMF use among patients with AD (aggregated population $N = 140$) found that the overall rate of herpes and other infections was 9.3% and 6.4%, respectively; the authors did not specify whether the herpes infections were herpes zoster or eczema herpeticum [69]. The mean duration of MMF treatment was 34.4 weeks in this analysis of mostly adult patients (mean age 38.2 years) [69]. A retrospective chart review of 20 adult patients receiving MMF for AD reported an HSV infection of the thighs and genitals in one patient (5.0%) and cutaneous *S. aureus* infections in two patients (10.0%), one with MRSA [70].

6.1.3 Biologics

Systemic biologic treatments targeting the type 2 pathway are among the advanced treatment options for AD [18]. Dupilumab, a fully human monoclonal antibody that binds to the shared α chain subunit of the IL-4 and IL-13 receptors and thereby inhibits the signalling of both cytokines, is the first targeted biological agent that received approval in major markets (Europe [including the UK] and the USA) for the treatment of moderate-to-severe AD [71–73]. Several pooled analyses showed no increase in the risk of serious or severe infections or HSV infections with dupilumab compared with placebo, including in children [71, 74, 75]. Although upper respiratory tract infections and nasopharyngitis were common adverse events (AEs) with dupilumab in clinical studies, the risk of these events and of urinary tract infections was no higher in adults or children receiving dupilumab than in those receiving placebo [71, 75]. Dupilumab was associated with a higher rate of conjunctivitis in both adults and children, with a significantly increased risk in adults when compared with placebo (risk ratio [RR] 2.64; 95% confidence interval [CI] 1.79–3.89; $p < 0.0001$) [75]. Of note, the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) 'conjunctivitis' represents conjunctivitis of unspecified or undetermined aetiology and defaults to the 'Infections and Infestations' system organ class in MedDRA [74]. The investigators' feedback provided through the data query process in these clinical trials indicated that most of the AEs coded under the PT 'conjunctivitis' were non-infectious, but otherwise of unclear aetiology [74]. The incidence rates of PT-defined conjunctivitis with specified bacterial or viral aetiology did not differ significantly between the dupilumab and placebo groups [74]. Real-world and long-term open-label studies also confirm the low rate of infections, including HSV, in adults and children with AD receiving dupilumab in clinical practice [76–82].

A recent meta-analysis that assessed the association of dupilumab therapy with risk of skin infections in patients with moderate-to-severe AD found that the RR for overall skin infections favoured dupilumab and was lower than placebo [83]. Pooled analyses of RCTs with dupilumab found a significantly reduced rate of skin infections in the dupilumab than the placebo group, with RRs of between 0.44 and 0.59, depending on the patient population (adults or children) and how the data were analysed (absolute incidence, exposure-adjusted incidence, any investigator-reported infections or adjudicated infections) [71, 74, 83, 84]. This includes a reduced rate of eczema herpeticum for dupilumab-treated patients compared with placebo, which was significant in adults (RRs 0.31–0.34) [74, 84], but did not reach statistical significance in children because of the smaller patient population (RR 0.50) [71].

Tralokinumab, an anti-IL-13 inhibitor [85], has been shown to improve skin lesions, pruritus and quality of life/sleep [16, 85], to have a favourable safety profile and a low risk of serious infections [71, 85–87]. A safety analysis of two phase 2 and three phase 3 RCTs of tralokinumab in moderate-to-severe AD found that the most frequent class of serious AE was infections and infestations, which was less common with tralokinumab compared with placebo, occurring in 0.4% and 1.1% of patients (1.3 versus 3.7 events [E] per patient-years [PY]; RR 0.3; 95% CI 0.1–1.0), respectively [88]. Moreover, the rates of skin infections requiring systemic treatment, eczema herpeticum, opportunistic infections and severe or serious infections were lower with tralokinumab compared with placebo [88]. An analysis of conjunctivitis data from the same five RCTs of tralokinumab in moderate-to-severe AD found a higher adjusted incidence of conjunctivitis (an AE of special interest) with tralokinumab compared with placebo (7.5% versus 3.2%; hazard ratio 2.4; 95% CI 1.5–3.8); the incidence rates for 'conjunctivitis bacterial' were 0.2% and 0.2% for tralokinumab and placebo, respectively, and for 'conjunctivitis viral' were 0.1% and 0.1%, respectively [89].

6.1.4 JAK Inhibitors

JAK inhibitors (e.g. abrocitinib, baricitinib and upadacitinib) are also approved for the treatment of moderate-to-severe AD. They simultaneously suppress the action of a number of different cytokines, including IL-2, IL-3, IL-4, IL-5, IL-10, IL-12, IL-13, IL-22, IL-23 and IL-31; IFN-α and IFN-γ; granulocyte colony-stimulating factor; erythropoietin; and thrombopoietin [90]. As a result, JAK inhibitors have a broader range of pleiotropic effects than biologicals [91], but also a broader range of possible AEs, including hematologic events such as anaemia and thromboembolism, hypercholesterolemia and increased levels of serum creatine kinase [92]. Although they have a rapid onset of action and effectively reduce AD symptoms and severity, they are associated with increased risks of viral infections [91]. Physicians need to consider patient age, medical history and comorbidities when determining the benefit:risk associated with JAK inhibitors for the treatment of AD [93]. Moreover, before starting treatment with oral JAK inhibitors, patients should undergo screening for chronic infections and a complete blood count should be conducted; the latter should be repeated, along with lipid profile evaluations, during treatment [94].

Data from patients treated with oral JAK inhibitors indicate that infections are among the most common AEs, although in RCTs, the rates of nasopharyngitis and upper respiratory tract infections are not always higher in the JAK inhibitor groups than the placebo groups [95]. However,

herpes viral infections do tend to occur at a higher rate in JAK inhibitor-treated patients compared with those receiving placebo [95]. Pretreatment assessment of infection risk and regular monitoring is required during treatment with JAK inhibitors [93].

Abrocitinib A meta-analysis of RCTs showed no increased risk of nasopharyngitis or upper respiratory tract infection with abrocitinib versus placebo [96]. Serious infections developed at an incidence rate of 3.80 and 1.28 per 100 PY in recipients of abrocitinib 100 mg or 200 mg, respectively, compared with 2.31 per 100 PY in placebo recipients, according to results of a pooled analysis of safety data from phase 2 and 3 trials [97]. The rates of herpes zoster infection among adults in the JADE REGIMEN study were 3.54 and 4.80 per 100 PY in the 100 and 200 mg abrocitinib groups, respectively, and 3.25 per 100 PY in the placebo group [98], whereas in studies comparing abrocitinib 200 mg with dupilumab (JADE COMPARE and JADE DARE), herpes zoster tended to occur at a higher incidence in the abrocitinib groups than the dupilumab groups [99, 100]. However, the overall incidence of infections was similar in the dupilumab and abrocitinib groups in the JADE COMPARE study [99]. In both JADE COMPARE and JADE DARE, acne/folliculitis was more common with abrocitinib than dupilumab, and one abrocitinib-treated patient in each study developed eczema herpeticum, compared with none of the dupilumab-treated patients [99, 100]. However, conjunctivitis (infectious, non-infectious or otherwise not specified) was more common with dupilumab in these studies [99, 100].

Baricitinib In an integrated safety analysis of data from baricitinib RCTs, the adjusted incidence rate of HSV infection with baricitinib 2 mg and 4 mg was 12.4 and 21.3 per 100 PY, respectively, compared with 9.4 per 100 PY with placebo [101]. The incidence of HSV infection was highest in the first 16 weeks of treatment and declined thereafter [101]. In the placebo-controlled dataset, the adjusted incidence rate of herpes zoster infection was 2.8 per 100 PY with baricitinib 2 mg (no herpes zoster events occurred with baricitinib 4 mg) and 1.0 per 100 PY with placebo, compared with 3.8 and 1.8 per 100 PY in the extended dataset with baricitinib 2 mg and 4 mg, respectively, and 2.3 per 100 PY in the dataset containing all baricitinib doses (1 mg, 2 mg and 4 mg) [101]. The adjusted incidence rate for eczema herpeticum was 0.2 and 1.4 per 100 PY in the baricitinib 2 mg and 4 mg groups, respectively, compared with 0.4 per 100 PY in the placebo group [101]. An integrated analysis of eight RCTs in adults with AD found that the rate of serious infections with baricitinib 2 and 4 mg was 1.4 and 2.7 per 100 PY, respectively; the rate in the placebo group was 2.1 per 100 PY [102]. The most common serious infections in the overall baricitinib group were eczema herpeticum (0.3 per 100 PY), cellulitis (0.2 per 100 PY), erysipelas, pneumonia and coronavirus disease 2019 (COVID-19) pneumonia (0.1 per 100 PY each) [102]. In a baricitinib 2–4 mg-extended data analysis set, among patients reporting skin infections that required antibiotic treatment, the incidence rate was lower in the 4-mg (2.5) versus the 2-mg (4.5) group and the more common PTs included skin infection, folliculitis, cellulitis and impetigo [102]. The available RCT, long-term extension and real-world evidence suggests that no clinically relevant or consistent dose-dependent response is associated with the 4 mg versus the 2 mg dose of baricitinib for AEs of special interest, except for infections, including herpes zoster, nor for the occurrence of venous thromboembolism, for which an imbalance between baricitinib and placebo has been observed during the placebo-controlled study periods in rheumatoid arthritis clinical trials [103]. In a RCT of children with AD, the incidence of infections (most commonly respiratory tract infections) was similar in those receiving baricitinib 2 or 4 mg or placebo for 16 weeks; no serious infections were reported [104].

Upadacitinib In RCTs of adolescents and adults with AD, upadacitinib was not associated with a significantly increased risk of infections compared with placebo [105–108]. In some instances, the incidence of serious infections was reported as < 1.0% in both upadacitinib 15 and 30 mg and placebo groups, while in others, serious infections developed at an incidence rate of 2.6–3.6 and 1.5–3.7 per 100 PY with upadacitinib 15 mg and 30 mg, respectively, versus placebo (2.7 per 100 PY) [105–108]. In an all-upadacitinib exposure analysis, serious infection rates were higher among patients aged 65 years and older who received upadacitinib 30 mg (8.2 E/100 PY) than among patients aged 65 years and older who received upadacitinib 15 mg (0 E/100 PY) or patients aged younger than 65 years who received either dose of upadacitinib (15 mg, 2.4 E/100 PY; 30 mg, 2.5 E/100 PY) [106]. In the 16-week analysis, the herpes zoster exposure-adjusted event rate (EAER) was higher with upadacitinib than with placebo, while in the all-upadacitinib exposure analysis, the herpes zoster EAER was higher with upadacitinib 30 mg than with upadacitinib 15 mg (5.2 E/100 PY versus 3.5 E/100 PY, respectively) [106]. EAERs of opportunistic infections (excluding tuberculosis and herpes zoster) were reported as eczema herpeticum or its synonymous Kaposi varicelliform eruption (including one case of oesophageal candidiasis reported with upadacitinib 30 mg); rates were similar across upadacitinib groups for both the 16-week and all upadacitinib exposure analyses, but higher than placebo in the 16-week analysis [95]. Overall, eczema herpeticum and herpes zoster have been the most commonly reported serious infections in association with upadacitinib treatment [105, 107, 108]. One Japanese patient developed *Pneumocystis jirovecii* pneumonia during treatment with upadacitinib [107]. In the randomised Heads Up trial,

which compared upadacitinib with dupilumab, upadacitinib was associated with slightly higher rates of upper respiratory tract infections (6.3% versus 3.8%), serious infections (1.1% versus 0.6%), eczema herpeticum (0.3% versus 0%) and herpes zoster (2.0% versus 0.9%), while the rate of nasopharyngitis was slightly higher in the dupilumab group (6.4%) than the upadacitinib group (5.7%) [109].

7 Treatment of Skin Infections

7.1 Bacterial Infections

Effective management of recurrent skin infections involves identifying and treating the underlying microbiologic agent, and implementing infection prevention measures. If left untreated, skin infections can become systemic and lead to life-threatening complications [24].

Topical and systemic antibiotics may be necessary to treat bacterial infections. However, antibiotics should only be used in clinically affected AD, as indiscriminate use increases the risk of developing antibiotic-resistant strains, which poses a therapeutic challenge [60]. Choice of treatment depends on local patterns of antibacterial resistance, particularly the prevalence of MRSA [110–112]. Culture of the causative pathogen is recommended to guide therapy, but empiric therapy is reasonable in uncomplicated cases or before culture results become available [113].

Table 2 summarises the guideline-recommended antibacterial options for empiric treatment of skin infections and when they are indicated [110–114]. Topical antibacterial agents can be used for the treatment of localised skin infections and decolonisation [13, 110, 112]. For uncomplicated, non-purulent skin infections, preferred empiric antibacterial treatments are usually oral β-lactam antibiotics, such as a penicillin or cephalosporin [13, 110–112]. In patients with AD and a skin abscess, oral antibiotics such as clindamycin, doxycycline, trimethoprim-sulfamethoxazole or linezolid can be considered [13]. Infections occurring in countries/regions with a high prevalence of MRSA require treatment with agents that are active against MRSA (e.g. trimethoprim-sulphamethoxazole, clindamycin, tetracyclines [doxycycline or minocycline], vancomycin or linezolid) and complicated infections may require agents active against Gram-negative and anaerobic pathogens (e.g. piperacillin-tazobactam) [110, 111]. MRSA-associated AD flares are difficult to treat with TCS because of corticosteroid resistance induced by staphylococcal superantigens [44]. In such a situation, prolonged use of corticosteroids may lead to skin atrophy and adrenal insufficiency, so alternative AD therapy should be considered.

7.2 Viral Infections

Antiviral drugs for the treatment of eczema herpeticum include acyclovir, valacyclovir, famciclovir and foscarnet for acute infections; acyclovir and valacyclovir are also used for long-term suppressive therapy [13]. Foscarnet is the recommended therapy for acyclovir-resistant HSV infections. The treatment for eczema coxsackium is similar to that of AD treatment, including skin hydration and moisturisation and use of TCS [12]. As molluscum contagiosum is usually benign, observation is generally recommended [13], but topical cantharidin or 5% potassium hydroxide solution can be used in paediatric patients [115].

7.3 Fungal Infections

The antifungal ketoconazole is an imidazole derivative that exhibits anti-inflammatory effects as well as anti-erythema and anti-oedema properties [52]. In a Swedish study, treatment with oral ketoconazole 200 mg/day for 2 months and 200 mg twice a week for another 3 months improved clinical AD severity and reduced the levels of total IgE, anti-*Malassezia* IgE and anti-*C. albicans* IgE [116]. Antifungal imidazoles with a more favourable safety profile include itraconazole and fluconazole. Terbinafine can be safely used in dermatophyte infections [52].

8 Prevention of Infections

Skin infections in patients with AD lead to higher healthcare resource utilisation and impose a heavy economic burden [15]. However, preventive measures to reduce skin infections, early treatment initiation, infection surveillance and patient education may reduce the occurrence of skin infections and consequently help in curbing the increasing healthcare costs [15].

Patients and their families should be educated about AD management and treatment to reduce the likelihood of future AD flare-ups and prevent and manage skin infections [117]. Of particular importance is education on the best practices for personal hygiene, such as regular bathing, use of gentle soaps and daily skin hydration and moisturising to protect the skin barrier and prevent microbial colonisation [13]. Regular bathing hydrates and cleanses the skin from scales, crusts, microbes, allergens and irritants, while twice-weekly bathing with dilute bleach (which has antiseptic and anti-staphylococcal properties) improves AD severity [16].

Daily application of fragrance-free moisturisers and effective control of AD lesions with topical anti-inflammatory medications can prevent disease deterioration and reduce the risk of infections.

Table 2 Recommended empiric treatment options for bacterial skin infections

Type of infection	Treatment			
	Children		Adults	
Localised skin infections:	Topical antibiotics (e.g. fusidic acid, mupirocin, retapamulin) [110]		Topical antibiotics (e.g. fusidic acid, mupirocin, retapamulin) [112]	
Uncomplicated superficial infections:				
Non-MRSA or regions where MRSA is not prevalent	Impetigo	Amoxicillin/clavulanic acid, flucloxacillin, oral cephalosporin (e.g. cephalexin, cephadroxil) [110]	Impetigo	Flucloxacillin, cephalosporin [112]
	Cellulitis/erysipelas	Oral first-generation cephalosporin (e.g. cephalexin) [110, 112]	Cellulitis	Oral beta-lactams (international) [111]; penicillin or cephalosporin or dicloxacillin or clindamycin (USA); penicillin (parenteral) or flucloxacillin or cloxacillin (Europe) [112]
Suspected MRSA or high MRSA prevalence[a]	Impetigo	Clindamycin, TMP-SMX, fluoroquinolones, tetracyclines (for children aged >8 years)	Impetigo/ cellulitis/ erysipelas	Glycopeptides, newer antimicrobials [111]
	Cellulitis/erysipelas	Oral TMP-SMX or clindamycin [110]		
Complex abscess or abscess with significant cellulitis:	Clindamycin or TMP-SMX [110]		Moderate	TMP-SMX or doxycycline (USA) [113]
			Severe	Vancomycin, daptomycin, linezolid, telavancin or ceftaroline (USA) [113]
			Broad-spectrum agents with Gram-positive, Gram-negative and anaerobic pathogen coverage may be required [111]	
Moderate/severe cellulitis:				
Non-MRSA or regions where MRSA is not prevalent	IV anti-staphylococcal penicillin or first-generation cephalosporin (e.g. cephalexin, cephalotin) for ≥ 48 h then switch to oral therapy with amoxicillin/clavulanic acid or cephalosporin (e.g. cephalexin) [110]		Vancomycin + piperacillin/tazobactam [113]	
Suspected MRSA or high MRSA prevalence[a]	IV TMP-SMX, vancomycin or clindamycin[b] for ≥ 48 h then switch to oral therapy with TMP-SMX or clindamycin[b] [110]		–	

Table 2 (continued)

Type of infection	Treatment		
	Children	Adults	
Complicated cellulitis:	IV vancomycin, teicoplanin or clindamycin[b]; add agent with Gram-negative and anaerobic coverage (e.g. piperacillin-tazobactam) if patient has risk factors,[c] including immunosuppression [110] Daptomycin (if aged > 12 years) or ceftaroline if MRSA suspected or prevalent	–	
MRSA infection:	Linezolid [110]	Oral	Clindamycin,[b] linezolid, TMP-SMX, a tetracycline (doxycycline, minocycline) or tedizolid [111]
		IV	Vancomycin, teicoplanin, tigecycline, linezolid, daptomycin, ceftaroline, dalbavancin or tedizolid [111, 113]
PVL-positive MRSA:	TMP-SMX, clindamycin or doxycycline [114]		
MDR Gram-negative infections:	Tailor therapy for likely pathogen and resistance pattern until culture results are available [127]		

IV intravenous, *MDR* multi-drug resistant, *MRSA* methicillin-resistant *Staphylococcus aureus, PVL* Panton-Valentine leucocidin, *TMP-SMX* trimethoprim-sulphamethoxazole
[a]Greater than 10–20%; [b]consider local clindamycin resistance before prescribing; [c]surgical drainage, bite or penetrating injury, foreign body, fracture or medical comorbidities

Prophylactic use of oral antibiotics is not recommended as it promotes the development of antibiotic-resistant microbial strains while having no positive impact on disease progression [118]. However, patients with bacterial skin infections will often benefit from topical decolonisation, as this reduces the risk of recurrent infection. For patients with AD and MRSA colonisation, the suggested treatment approach includes nasal mupirocin twice daily for 10 days and a diluted bleach bath (62.5 mL of 6% sodium hypochlorite per bathtub of water) 15 min daily for 5 days, then twice weekly, along with TCS/TCI application on AD lesions and moisturiser on unaffected areas [44].

Given the increased incidence of herpes zoster in patients receiving JAK inhibitors, vaccination against herpes zoster before starting JAK inhibitors is recommended [119–125]. If live vaccines are used, they should be administered 3–4 weeks before initiating JAK inhibitor therapy [119, 126].

9 Conclusions

Patients with AD are at increased risk of developing skin infections due to impaired skin barrier function and a dysregulated immune system; extracutaneous and systemic infections may also represent a concern. Recurrent bacterial infections can favour disease chronicisation and cause disease flares with significant morbidity, and possible mortality (in the case of eczema herpeticum), in patients with AD. For the management of infections in patients with AD, it is important to identify and treat the underlying infection, optimise AD treatment to improve skin barrier function and immune system regulation and implement infection prevention strategies. The risk of infection should also be considered when selecting topical or systemic immunosuppressive therapies, as some of these agents can increase the risk of viral infections.

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Declarations

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Conflicts of Interest Maria Esposito has served as a speaker or board member for AbbVie, Almirall, Amgen, Eli Lilly, LEO Pharma, Janssen, Novartis, Pfizer, Sanofi and UCB. Maria Concetta Fargnoli has served as an advisory board member for AbbVie, LEO Pharma, Novartis and Sanofi. Caterina Foti has acted as a speaker, consultant and advisory board member for AbbVie, Amgen, LEO Pharma, Novartis and Sanofi.

Giampiero Girolomoni has served on boards for, received research grants from and received personal fees/honoraria for lectures from AbbVie, Almirall, Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Galderma, Janssen, LEO Pharma, Merck Serono, Novartis, Pfizer, Pierre Fabre, Samsung Bioepis and Sanofi. Paolo Matruglio and Elena Nicoli are employees of Sanofi and may hold shares and/or stock options in the company. Maddalena Napolitano has acted as speaker, consultant and advisory board member for AbbVie, Amgen, Eli Lilly, LEO Pharma, Pierre Fabre and Sanofi. Paolo Romita declares no potential conflict of interest.

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