Staphylococcus aureus is the most common infective agent of the skin in patients with atopic dermatitis. Roughly 80% to 90% of atopic dermatitis patients are colonized with *S. aureus* compared with only 5% of healthy controls. Disease activity and severity have been associated with *S. aureus* density, with acute lesions having more *S. aureus* than chronic lesions, unaffected atopic skin, and normal nonatopic skin. Extensive research has revealed *S. aureus* colonization to be both a consequence and a cause of the underlying inflammation of atopic dermatitis.

*S. aureus* binds to the superficial epidermis largely via fibronectin and fibrinogen, extracellular matrix proteins that are exposed when the epidermis is disrupted by inflammation or scratching. The prominent Th2 cytokine, IL-4, has been shown to induce production of fibronectin by skin fibroblasts. Numerous studies during the past several years have demonstrated decreased presence of resident cutaneous antimicrobial peptides in atopic dermatitis (AD) compared with psoriasis, including beta-defensins hBD2 and hBD3, cathelicidin LL-37, and calgranulins.

*S. aureus* contributes directly to AD inflammation in a variety of ways. Staphylococcal enterotoxin B (SEB) and alpha-toxin act as superantigens, leading to massive stimulation of T cells and production of IgE-specific antibodies that contribute to mast cell degranulation and symptoms of pruritus and acute inflammation. SEB and alpha-toxin are also more potent stimulators of IL-22 secretion in patients with AD compared with patients with psoriasis and healthy controls, which may help explain the role of *S. aureus* in eczema flares.

**STAPHYLOCOCCAL ‘SUPERINFECTIONS’**

As staphylococcal colonization is nearly universal in AD, superinfection of skin lesions is also common. Risk factors for severe impetiginized eczema include poorly controlled AD with involvement of significant body surface area. Development of pustules, crusting, erythema, edema, or local lymphadenopathy are all clinical signs that a patient with AD has developed a secondary bacterial infection, most commonly with *S. aureus* or *Streptococcus pyogenes* (see Figure 1).

While methicillin-resistant *S. aureus* (MRSA) is becoming more common, clinical and epidemiologic factors are not always reliable in distinguishing MRSA from methicillin-sensitive *S. aureus* (MSSA) in patients with AD. The most important clue may be lack of improvement while taking beta-lactam antibiotics such as cephalaxin.

Diagnosis and antibiotic susceptibility profiles are best obtained from culture of clinically infected lesions. While it may seem intuitive that AD patients should be more susceptible to developing MRSA infections because of their repeated exposure to antibiotics, several recent studies suggest that AD patients are not at increased risk for developing MRSA and may, in fact, have a lower risk than general pediatric patients.

While such data appear reassuring, AD patients can and do become colonized with MRSA, which can lead to flaring of AD or progress to true infection. Monitoring bacterial cultures in patients with refractory to standard oral
antibiotic therapy is necessary to guide their therapy effectively.

**CONTROLLING STAPH COLONIZATION**
While colonization is an obvious risk factor for infection, decreasing or eradicating *S. aureus* colonization is challenging. A recently published review on interventions to reduce *S. aureus* colonization found that both topical corticosteroids and antibacterial agents can decrease the *S. aureus* bacterial load on the skin of patients of AD, but found no convincing evidence that a decrease in colonization leads to demonstrable clinical improvement. Additionally, patients quickly revert to previous levels of colonization when interventions are discontinued.12,13 Included in this review was a recent report demonstrating improvement in the severity of moderate/severe AD with use of intranasal mupirocin (twice daily for 5 consecutive days per month) and diluted bleach baths (one-half cup of common household bleach diluted in approximately 40 gallons of water for a final bleach concentration of 0.005%, used as a 5- to 10-minute soak twice weekly). However, even in these patients, *S. aureus* was cultured from both the skin and the nares of patients at the end of treatment. Larger, high-quality randomized controlled trials are needed to better define the benefits and risks of antistaphylococcal treatment.

**EFFECTIC OF ANTIBIOTICS**
In patients with AD that is resistant to appropriately applied topical anti-inflammatory agents, and in those who have clinical signs suggestive of elevated bacterial burden or infection, the simple addition of short courses of appropriate antibiotics that target typical gram-positive infectious agents (first- or second-generation cephalosporins, amniopenicillins) often leads to rapid and dramatic improvement in cutaneous lesions, without any other alteration in treatment. In such AD patients, unless MRSA is suspected, it is reasonable to treat empirically with the above agents, reserving bacterial cultures for patients who do not respond.

If MRSA is present or suspected because of clinical appearance, then appropriate antibiotics such as trimethoprim/sulfamethoxazole or clindamycin can be used. Topical antibiotics such as mupiricin can be helpful for superficial or mild limited skin infections, or for decreasing colonization at body sites that are common reservoirs of *Staphylococcus*, such as the nares, perineum, or axilla.14 Diluted bleach baths may also be employed with great success and minimal complications (as they frequently are by the authors) in patients requiring repeated antibiotic courses.

Recently, the role of group A streptococcus (GAS) in skin and soft tissue infections in AD patients has been highlighted.15 Importantly, in a retrospective review, the presence of GAS was associated with a higher incidence of fever, cellulitis, and hospitalization in patients with AD. In a number of patients with proven GAS infection, the clinical lesions mimicked disseminated herpes simplex virus (HSV). Additionally, while standard MSSA antibiotics are also effective against GAS, trimethoprim/sulfamethoxazole — which is being used more frequently in suspected MRSA infections — is not reliably effective for GAS. This report again highlights the need to follow cutaneous bacterial cultures in difficult or treatment-resistant AD patients.15

**VIRAL INFECTIONS**
Patients with inflammatory skin disease such as AD, Darier-White disease, Hailey-Hailey disease, certain ichthyoses, and pemphigus foliaceous are also susceptible to cutaneous viral infections.16
Some of the same factors that increase the risk for bacterial infection also contribute to viral infections such as HSV, herpes vaccinatum, and molluscum contagiosum. These factors include disrupted epidermal barrier leading to enhanced viral penetration; decreased antimicrobial peptides; and prominence of T-helper type 2 (Th2) cytokines. These also contribute to viral infections such as HSV, herpes vaccinatum, and molluscum contagiosum.

Eczema Herpeticum

HSV is the most common viral co-infection in AD patients. Disseminated cutaneous infection with HSV is termed eczema herpeticum (EH). Past estimates for EH frequency in patients with AD were roughly 3% to 15%, although a recent large population study suggested a higher rate, closer to 50%. Patients who developed EH were more likely to have severe skin disease, earlier age of onset, more severe Th2 polarity, greater serum IgE levels, greater allergen sensitization, and significantly higher incidence of S. aureus infections.17

HSV reactivation in response to sunlight, trauma, stress, or immunosuppression is often preceded by a prodrome of burning or pruritus and leads to “outbreaks” in the distribution of the involved nerve.

EH is believed to develop more commonly from primary HSV infection rather than reactivation. Classically, HSV presents as grouped monomorphic vesicles on an erythematous base with rupture of the vesicles, producing punched out ulcers (Figure 2, see page e2). In patients with poorly controlled AD, EH may be difficult to detect or misdiagnosed as a bacterial infection (especially GAS)14 or contact dermatitis; any flare of AD should prompt examination for EH. Systemic symptoms such as fever, malaise, and poor appetite are common.18

EH may have severe complications such as keratoconjunctivitis, leading to blindness, meningitis, encephalitis, and secondary bacterial sepsis. Before the availability of acyclovir, EH mortality approached 75%. Viral culture has been considered the gold standard for diagnosis but is limited by its low sensitivity. Yields are highest when the viral culture is obtained from the base of a new vesicle less than 48 hours old. A Tzanck smear is quick and easy to perform, but specificity and sensitivity are highly variable; multinucleated giant cells and intranuclear inclusions are seen with Giemsa or Wright stain. Serology is most useful in differentiating primary HSV infections from reactivation using comparison of acute and convalescent titers separated by 2 to 4 weeks.

Polymerase chain reaction (PCR) and direct fluorescence antigen (DFA) detection are newer methods and are less studied in cutaneous HSV. Both methods have high sensitivity and allow differentiation of HSV-1 and HSV-2, but DFA is less expensive, more widely available, and is the preferred molecular technique.18 Histologic examination is less commonly performed and may show an intraepidermal vesicle, multinucleated cells, nuclear molding, or cells with steel gray nuclei. Because histologic exam cannot differentiate HSV-1, HSV-2, or varicella, the diagnosis is often best established with a combination of the above methods.

HSV-1 and HSV-2

In the clinic, the diagnosis of disseminated HSV infection can require a high index of suspicion. Some cases may be subtle clinically, which may explain the variation in estimated EH incidence. It is less clear what the associated morbidity is from milder EH outbreaks, but given the speed with which HSV infection can spread or become severe in these patients, an aggressive approach is essential.

When HSV is confirmed in an AD patient, often, empiric antiviral therapy is initiated at this time, as waiting for viral culture/PCR results without treatment could lead to greater morbidity. Oral acyclovir is the treatment of choice and carries a pediatric indication. While neither valacyclovir nor famciclovir carries an indication for use in children and only come in pill forms, recent shortages in acyclovir have necessitated their use; they have been shown effective and safe in pediatric patients.20

Hospitalization with intravenous acyclovir may be necessary in rapidly pro-
gressing or severe cases. Extreme caution must be taken in cases with facial and periocular involvement, given the risk for corneal scarring from HSV keratoconjunctivitis. Topical antiviral therapy has no place in the treatment of active EH due to complete lack of established efficacy. Viral culture with investigation of antiviral sensitivities is important in patients resistant to treatment, as thymidine kinase-resistant HSV has been reported in AD patients.21

**Molluscum Contagiosum**

This poxvirus is distinct from vaccinia and variola. Molluscum contagiosum (MC) infection is common in childhood, appearing with greater frequency and severity in AD patients.

MC lesions typically appear on affected AD skin but may also affect uninvolved skin, possibly due to autoinoculation. Umbilicated, skin-colored papules are the classic findings. Secondary reactions to MC infection are common. A secondary “molluscum dermatitis” occurs in many cases and may be difficult to discern from the surrounding eczematous patches (Figure 3, see page e3). There are no associated systemic findings.

Diagnosis of MC is usually made clinically with dermoscopy, helping to highlight the central umbilication in questionable cases. If the diagnosis remains in question, biopsy of a lesion will show epidermal invagination and the pathognomonic Henderson-Paterson bodies. Management of MC in the AD patient can be difficult. The presence of active dermatitis can lead to easier spread of the virus itself and can also interfere with the assessment and treatment of lesions.

Often, a reasonable initial approach is to calm any existing AD/MC dermatitis with topical anti-inflammatory agents (eg, 2.5% hydrocortisone) in addition to directly treating the MC. A variety of therapies have been employed to treat MC. These differ in efficacy and in the amount of patient discomfort associated with treatment. Curettage of lesions can be effective but is often uncomfortable and even frightening for younger patients.

Cryotherapy with liquid nitrogen is similarly effective but uncomfortable. Topical cantharidin, a topical vesicant made from the Chinese blister beetle, has been used as a relatively painless and effective treatment for decades. However, reactions to the agent are less predictable and it cannot be obtained from any pharmacy in the US because it lacks FDA approval. Other agents such as topical tretinoin or oral cimetidine are less well studied.22

**ECZEMA VACCINATUM**

Eczema vaccinatum (EV) results from the dissemination of the vaccinia virus (VV), a live virus used in the smallpox vaccine. Currently, a past history of AD or active AD are contraindications to vaccination due to concern over EV. During the decades of widespread smallpox vaccination in the US, EV occurred in roughly 10 to 38 cases per million, with fatality rates ranging from 30% to 40% in untreated patients, with most deaths occurring in small children.23,24 Since the reinstitution of smallpox vaccination of US military personnel and designated public officials in 2002, a single case of EV has been reported, occurring in a 28-month-old male with severe AD who contracted the virus from his recently vaccinated military father. The patient’s father had been vaccinated no fewer than 21 days before exposing his family, a time when in most, the virus would no longer have been present. The father’s personal history of AD may help explain his prolonged viral shedding. The patient’s mother also developed signs of vaccinia infection, confirmed with PCR, and his siblings showed positive serology.23,25

**EV Presentation and Diagnosis**

EV presents with a characteristic distribution involving the face, neck, antecubital and popliteal fossae; it tends to present most commonly in areas of active dermatitis, although it can also involve normal skin and become confluent and disseminated. EV begins as papules that evolve into prominently umbilicated vesicles or pustules that may form crusts, often on erythematous and edematous bases. Importantly, all the lesions are in the same stage of development, and in untreated patients, may come in periodic crops. Lesions typically resolve in 21 days, leaving depressed scars that may be severe.26 Vesicular lesions in an AD patient with possible exposure to a smallpox/vaccinia vaccinee should raise suspicion of EV. Diagnosis is made most readily with the use of PCR, which can differentiate vaccinia, variola, and other orthopoxviruses. Cytopathic effect can be noted on viral culture, but this is not specific for vaccinia. Guarnieri bodies, or type-B inclusions, are eosinophilic blobs noted in the cytoplasm of cells infected with poxvirus that can be seen on histologic examination.

**CONCLUSION**

Cutaneous infections frequently complicate the picture of inflammatory skin diseases. Because of the higher likelihood of developing disseminated or more severe disease compared with normal or even psoriatic skin, cutaneous infections should be taken seriously in the pediatric patient population. Goals of therapy should be aimed at properly treating the infection and gaining improved control of the underlying inflammatory disease to reduce risk for recurrent infection.

**REFERENCES**


