Infectious Complications in Atopic Dermatitis

Di Sun, MD, MPH[a], Peck Y. Ong, MD[a,b,*]

KEYWORDS

• Atopic dermatitis • *Staphylococcal aureus* • Eczema herpeticum • Keratinocytes • Innate

KEY POINTS

- Infections are a major complication of atopic dermatitis.
- These complications include *S aureus* infections, eczema herpeticum, eczema coxsackium and eczema vaccinatum.
- An understanding of the mechanisms of these infections is important for prevention and treatment.
- The article includes clinical pearls for clinicians in the recognition and management of these complications.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease with a prevalence of 10% to 20% in children and 1% to 3% in adults in industrialized countries.[1] This common condition arises from the interplay of genetic and environmental factors that culminates in skin barrier defects and an inappropriate immunologic response.[2] Characterized by intensely pruritic lesions that can lead to sleep disruption, AD is associated with inferior school performance, poor self-esteem, and familial stress.[3,4] Despite these sizable comorbidities, the major complication of AD remains infection.

PATHOPHYSIOLOGY OF INFECTIOUS COMPLICATIONS

The infectious complications of AD are rooted in its pathogenesis. The interaction between the immune system, environment, and skin barrier defects initiates an inflammatory cycle that alters the skin's innate immunity and microbiome (**Fig. 1**), leading to infectious complications.

Disclosure: Dr P.Y. Ong has received funding from National Institute of Allergy and Infectious Disease (UAI117673, 20096801) (Atopic Dermatitis Research Network) and Regeneron (Dupilumab).

[a] Department of Pediatrics, Keck School of Medicine, University of Southern California, 1975 Zonal Ave, Los Angeles, CA 90033, USA; [b] Division of Clinical Immunology and Allergy, Children's Hospital Los Angeles, 4650 Sunset Boulevard, MS 75, Los Angeles, CA 90027, USA
* Corresponding author.
E-mail address: pyong@chla.usc.edu

Immunol Allergy Clin N Am 37 (2017) 75–93
http://dx.doi.org/10.1016/j.iac.2016.08.015
immunology.theclinics.com

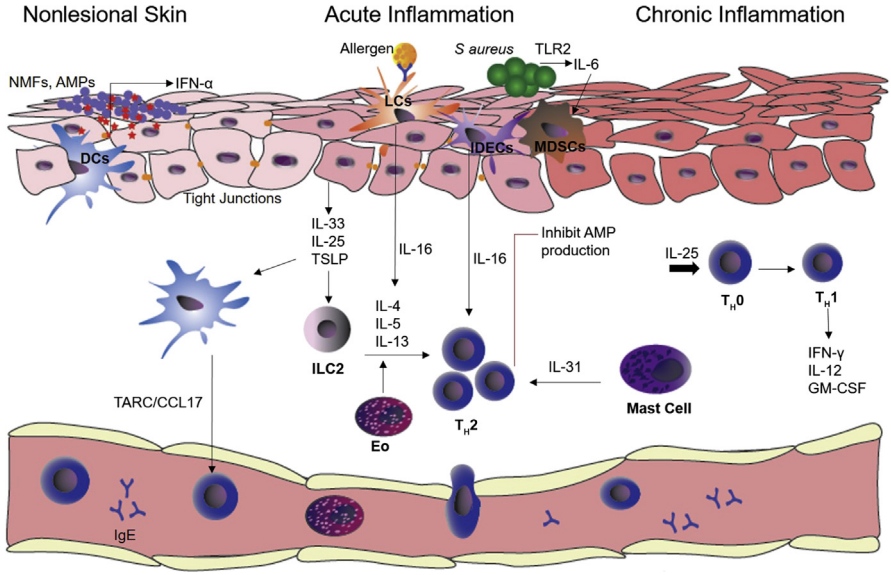

Fig. 1. Pathophysiology of skin infections in AD. ILC2, group 2 innate lymphoid cells. Eo, eosinophil; NMF, natural moisturizing factor.

Skin Barrier Defects

The outermost layer of the epidermis, the stratum corneum (SC), a cornified squamous epithelium that prevents water loss and guards against entry of foreign substances, is defective in AD.[5] A "bricks and mortar" structure, the SC is composed of dead SC cells held by a mortar of cornified cell envelope comprised of a protein/lipid polymer just beneath the cytoplasmic surface of the cells.[6] Defects in the layer are associated with AD: skin in AD patients has significantly thinner SC than healthy controls and transepidermal water loss studies demonstrate increased water loss in affected sites—a hallmark of AD—with increasing transepidermal water loss correlating with increasing AD severity.[7,8]

This skin barrier defect has been linked to mutations in filaggrin gene (*FLG*).[9] Meta-analyses of studies evaluating the association between *FLG* mutations and AD found an odds ratio (OR) of 4.78.[10] This association is likely due to the important role of filaggrin in interacting with the keratin cytoskeleton to excrete lipid lamellae to form the cornified envelope comprising the mortar structure of the SC.[2] Impaired excretion of the envelope results in compromise of the skin barrier. Filaggrin also helps maintain cell-to-cell integrity; those with *FLG* defects have decreased tight junctions and corneodesmosin density—proteins needed to main connections between cells.[11] The filaggrin breakdown products, pyrrolidone carboxylic acid and urocanic acid, are also natural moisturizing factors that maintain skin moisture and acidify skin-surface pH, which prevent activation of serine proteases and kallikrein.[12] Defects in *FLG* thus result in dry skin and activation of these downstream enzymes that inhibit lamellar excretion via activation of protease-activated receptor type 2, degrade tight junctions and corneodesmosomes, and down-regulate ceramide synthesis.[9] The rise in pH also promotes proliferation and adhesion of *Staphylococcus aureus*.[13–16] Moreover, activation of kallikrein produces the pro–helper T-cell (T_H), T_H2, response without allergen priming, thereby interacting with the immune system to promote an inflammatory response.[17]