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MINIREVIEW

The Role of *Staphylococcus aureus* in Secondary Infections in Patients with Atopic Dermatitis (AD)

ANETA BUDA and JACEK MIĘDZOBRODZKI*

Department of Microbiology, Faculty of Biochemistry, Biophysics and Biotechnology,
Jagiellonian University, Krakow, Poland

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Abstract

Staphylococcus aureus colonizes the mucous membrane of the nasal vestibule of a significant number of healthy people. These microorganisms are opportunistic pathogens, that in favorable conditions, may cause infections of various course, location or manifestation. Secondary infections emerge in cases when other risk factors contribute to such a change. One of the diseases during which *S. aureus* changes its saprophytic character to a pathogenic one is atopic dermatitis (AD), an allergic skin condition of a chronic and recurrent nature. Patients with AD are highly predisposed to secondary staphylococcal infections due to active *S. aureus* colonization of the *stratum corneum*, damage of the skin barrier or a defective immune response. Microorganisms present in skin lesions destroy the tissue by secreting enzymes and toxins, and additionally stimulate secondary allergic reactions. The toxins secreted by strains of *S. aureus* also act as superantigens and penetrate the skin barrier contributing to a chronic inflammation of the atopic skin lesions. The *S. aureus* species also releases proinflammatory proteins, including enzymes that cause tissue damage. When initiating treatment it is particularly important to properly assess that the onset of the secondary bacterial infection is caused by *S. aureus* and thus justifying the inclusion of antibiotic therapy. Depending on the severity and extent of the staphylococcal infection, topical antibiotics are used, usually mupirocin or fusidic acid, or general antibiotic treatment is introduced. Another therapeutic strategy without antibiotics has given a positive effect in patients.

Key words: *Staphylococcus aureus*, atopic dermatitis (AD), opportunistic infections, secondary staphylococcal infections, skin lesions

Introduction

Atopic dermatitis (atopic eczema, dermatitis eczema, eczematous dermatitis, neurodermititis), (latin: *dermatitis atopica*), also known as endogenous eczema is a chronic, relapsing inflammatory skin disease, which is characterized by skin lesions. The pathogenesis of AD is complex and still not fully understood. It is considered that all the interactions that occur between the genetically determined impairment of the structure and function of the epidermal barrier, the dysregulated immune and inflammatory response, environmental factors and infectious agents are engaged in the pathophysiology of AD (Ring *et al*., 2012). Lichenification of the skin and pruritis, a very burdensome symptom, are distinctive manifestations of AD. The Hanifin and Rajka diagnostic criteria for AD are used to diagnose this skin disease (Hanifin and Rajka, 1980).

Research conducted in recent years has brought two hypotheses to light that attempt to explain the pathogenesis of atopic dermatitis. The first hypothesis assumes that the initiating cause of the development of AD are immunological disorders. The initial stage of AD is characterized by a dominance of Th2 cells that secrete proinflammatory cytokines IL-4, IL-5, IL-13 and IgE. However, AD begins to shift into the chronic phase, Th1 cells begin to dominate. These immune aberrations cause inflammatory changes in the epidermis triggering epidermal barrier dysfunction. This hypothesis is called the "inside-to-outside hypothesis". Another concept presumes that there is a fundamental dysfunction of epithelial cells and so an impaired epidermal barrier. The presence of this defect may lead to the penetration of the epidermal barrier by allergens or other irritants inducing a secondary immune response in the skin. This hypothesis is named the "outside-to-inside hypothesis". Since the discovery of the mutation in the filaggrin (FLG) gene in a significant number of patients, researchers have begun to favour the second hypothesis as an explanation for the onset of AD (Palmer *et al*., 2006; Cork *et al*., 2009; Werfel, 2009; Bussmann *et al*., 2011).

* Corresponding author: J. Międzobrodzki, Department of Microbiology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland; **e-mail: jacek.miedzobrodzki@uj.edu.pl**

It is also known that dendritic cells (specifically Langerhans cells), keratinocytes, mast cells and eosinophils are key elements in the pathogenesis of AD. Dysfunction of these regulatory cells initiates a pathological process that leads to the development of symptomsin the course of atopic dermatitis (Werfel, 2009; Boguniewicz and Leung, 2011).

Epidemiology

Statistically, atopic dermatitis is one of the most common allergic conditions after hay fever and asthma. It affects nearly 30% of children and approximately 5% of adults who often develop secondary bacterial infections of the skin lesions (Nakamura *et al*., 2013). AD is an allergic condition that is showing a steady annual growth rate of 4% on a global scale. About 3% of adults suffer from AD in Poland. Residents of larger cities are more prone to develop AD than residents of rural areas (Sybilski *et al*., 2015). AD is often accompanied by other allergic conditions such as atopic asthma or allergic rhinitis (Lis *et al*., 2002).

The course of AD can be divided into the following phases: infantile, childhood, adolescent and adult. These phases are distinguished by the location of skin lesions and course of the disease (Nutten, 2015). Observations show a higher prevalence of AD development in women than in men (Sybilski *et al*., 2015).

Colonization of healthy skin by microorganisms

Changes in the microflora of patients with AD. The composition of a person's normal microflora depends on the colonized area of the human host. Generally however, the human microbial population consists of coagulase negative staphylococci, mainly *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*; *Propionibacterium acnes*, and yeasts of the genus *Malassezia*, most commonly the *Malassezia restricta* and *Malassezia globosa* species. All of these microorganisms are present on the skin surface and in skin folds as well as in hair follicles. Smaller populations of other species may also be identified: *Micrococcus* sp., *Aerobacter* sp. and *Proteus* sp. and in less abundance others (Wiburg *et al*., 1984; Grice and Serge, 2011).

The opportunistic pathogen *Staphylococcus aureus* may be a component of the normal microbial flora of the skin and according to various authors, it may be found in 5% to 100% of healthy individuals. However, a vast majority of people are either permanent or transient carriers of this species in the nasal vestibule (Kloos and Schleifer, 1986).

A characteristic feature of patients with AD is the abundant presence of bacteria of the genus *Staphylococcus* in comparison to healthy individuals (Table I). Results show an increased number of coagulase negative staphylococci that belong to the normal microflora as well as of *S. aureus* that triggers immune responses. Strains of the bacterial species *S. aureus* are present on the skin of patients and/or in the mucous membrane of the nasal vestibule of more than 80% of patients with disease exacerbation and in remission (Soares *et al*., 2013). The number of *S. aureus* cells in AD patients is 100-fold higher than in healthy individuals (Gloor *et al*., 1982; Hauser *et al*., 1985).

S. epidermidis strains found on human skin serve a protective function against *S. aureus* strains. The basis for this phenomenon is the antagonistic effect of *S. epidermidis* which produces antimicrobial peptides. Their task is to fight against other bacteria and to stimulate keratinocytes to produce antimicrobial peptides. The abundant number of *S. aureus* cells on the skin cause an increase in population of *S. epidermidis*, which is an additional burden for the skin (Cogen *et al*., 2010).

Table I
Microorganisms from the normal skin and from patients with atopic dermatitis (AD), in alphabetical order.

Microflora of the skin	normal	AD
Acinetobacter spp.	+	+
Aerobacter sp.	+	–
Brevibacterium spp.	+	+
Candida spp.	+	+
Corynebacterium spp.	+	+
Escherichia coli	+	+
coagulase-negative staphylococci	+	++
Klebsiella spp.	+/–	+
Malassezia spp. (*Pityrosporum* spp.)	+	++
Micrococccus spp.	+/–	+/–
Propionibacterium spp.	+	+
Proteus sp.	+/–	+/–
Salmonella spp.	+/–	+
Staphylococcus aureus	+	++
Streptococcus spp.	+/–	+

S. aureus, a pathogenic species – determinants of pathogenicity

S. aureus is capable of synthesizing virulence factors as well as of their extracellular release. These virulence factors demonstrate high biochemical activity. *S. aureus* exhibits a high resistance to a wide range of antibiotics and other antimicrobial agents.

S. aureus has the ability to adhere to components of the extracellular matrix. Adherence is mediated

by surface adhesins that belong to the MSCRAMM (microbial surface components recognizing adhesive matrix molecules) family of proteins. Examples include fibronectin-binding proteins A and B, (FnBPs), collagen-binding proteins, (CnBPs) and fibrinogen-binding proteins (Fb-BPs), (Gordon and Lowy, 2008; Schlievert *et al*., 2010). *S. aureus* produce numerous virulence factors that enable them to penetrate the host's protective barriers, spread into tissue and initiate infection, including the following: alpha-, beta-, delta-, gamma-hemolysins, lipase, serine proteinase (V8 protease) aureolysin (metalloproteinase), hyaluronidase, coagulase, fibrinolysin, staphylokinase, leukocidin, especially the Panton-Valentine leukocidin. Other important virulence factors include enterotoxins (*i.e*. SEA, SEB, SEC, SED, SEE and others), the Toxic shock syndrome toxin-1 (TSST-1) and epidermolytic toxins (Bukowski *et al*., 2010). The pathogenicity of *S. aureus* also depends on the presence of cell wall components such as: protein A, clumping factors (ClfA and ClfB) and teichoic acids and the bacterial capsule polysaccharide. Other notable virulence factors include peptidoglycan and lipoteichoic acid – major constituents of the cell wall (Gordon and Lowy, 2008; Kobayashi and DeLeo, 2009; Krishna and Miller, 2012; Otto, 2014).

S. aureus as an allergen

Colonization of the skin by *S. aureus* in AD causes the immune system to over-respond to their presence, has a toxic effect on keratinocytes and stimulates lymphocytes to secrete interferon (IFN) which consequently leads to the development of the chronic form of AD. The bacteria themselves as well as their excreted metabolites induce the activation of T lymphocytes, macrophages and antigen-presenting cells, leading, inter alia, to the increased production of immunoglobulins E (IgE) and G (IgG). An elevated level of IgE is one of the distinctive signs of an immune response to an allergen. Antistaphylococcal immunoglobin E (IgE) has been identified and measured in patients with AD and its level correlates with the severity of the disease (Adamek-Guzik *et al*., 2001; Ide *et al*., 2004).

Furthermore a high level of IgE in patients is associated with the coexistence of asthma, the length of the AD duration, as well as the severity of pruritus. Additionally, these responses trigger basophil activation (Reginald *et al*., 2011; Petry *et al*., 2012).

Secondary infections with *S. aureus* as a consequence of AD

Secondary infections, also known as superinfections are usually bacterial, fungal or viral infections that occur in the presence of an existing condition. Patients with AD are strongly predisposed to the development of secondary staphylococcal infections as a result of colonization of the *stratum corneum* by the *S. aureus* species, damage to the skin barrier or a defective immune response. Due to the fact that *S. aureus* is present in the skin of almost all patients with AD, the mere presence of these bacteria is not a sufficient criterion for the onset of a secondary infection in skin lesions (Lübbe, 2003; Gong *et al*., 2006).

Skin lesions in AD undergo impetiginization and become crusted, honey-coloured and weeping as a result of secondary infection. Pustules may sometimes appear on the skin of hands and feet (Lübbe, 2003).

The types of infections in atopic dermatitis

Patients with atopic dermatitis are exposed to infections caused by various groups of etiological factors as presented in Table I. The most common include: bacterial infections caused by various species of bacteria with infections predominantly caused by the *S. aureus* species; fungal infections, primarily caused by dermatophytes, *Malassezia* spp. and *Candida* spp., and viral infections, dominantly caused by the herpes simplex virus (HPV) and human parvovirus (HPV). However, epidemiological studies clearly indicate that greatest significance is given to infections caused by *S. aureus* or fungi (Ring *et al*., 1992; Lübbe, 2003; Sonesson *et al*., 2013).

Factors favoring *S. aureus* infections in patients with AD

The predisposition of patients with AD to the development of staphylococcal infections is associated with a defective epidermal barrier, raised adhesion activity of bacteria to skin cells, impaired elimination of these bacteria and impaired innate and acquired immunity. Abnormal lipid composition of the *stratum corneum*, sphingosine level reduction, altered skin pH values, low concentrations of IgA sweat gland secretions and a shortage of antimicrobial peptides, specifically cathelicidin LL-37, beta-defensins HBD-1, HBD-2, and HBD-3, as well as dermacidin, all of which have been reported in patients with AD, promote skin colonization by *S. aureus* and seriously hinder the elimination of the infectious agent. Additionally, scratching the affected area and use of various topical treatments makes patients with AD particularly vulnerable and prone to infections (Roll *et al*., 2004; Boguniewicz and Leung, 2011).

Virulence factors produced by *S. aureus* in atopic dermatitis. Microorganisms that are present in skin lesions cause tissue damage by secreting enzymes and toxins as well as by stimulating secondary allergic

responses. Bacterial strains, particularly *S. aureus* strains, isolated from the skin of patients with AD are capable of producing many toxins and enzymes such as aureolysin, serine proteinase (V8 protease) or phenol-soluble proteins known as Phenol-soluble modulins (PSMs), (Baran-Raunstrup *et al.* 1998; Międzobrodzki *et al.*, 2002; Rojo *et al.*, 2014). Staphylococcal enterotoxins, the toxic shock syndrome toxin-1 and other toxins such as alpha-toxin, play an important role in the development and sustenance of secondary infections in atopic skin lesions (Bogdali *et al.*, 2016). Enzymes and other substances that are secreted by bacteria into the tissue of the skin lesions during secondary infections are equally important. The structural components of bacterial cells such as the cell wall peptidoglycan or the staphylococcal pigment are also present significance (Lomholt *et al.* 2005; Soares *et al.*, 2013).

Staphylococcal superantigens – mechanism of action. *S. aureus* strains isolated from the skin of patients with AD release toxins, such as staphylococcal enterotoxins A, B, C (staphylococcal enterotoxin A, B, C) and the Toxic shock syndrome toxin-1 (TSST-1) which penetrate the epidermis and interact with the various cell types involved in the immune response, leading to an inflammatory response orchestrated by T cells. These virulence factors act as superantigens and are produced by almost 70% of *S. aureus* strains (Abeck and Mempel, 1998; Leung *et al.*, 2004; Soares *et al.*, 2013). Staphylococcal superantigens (SSAg,) trigger T cell activation by binding non-specifically to the T cell receptors (TCR) without the need for antigen presentation (Otto, 2014). Superantigens penetrate the skin barrier and contribute to the development of a chronic inflammation in the atopic skin lesions. Toxins stimulate lymphocytes to excessively produce cytokines such as IL-4. Additionaly, they promote the production of IgE against SSAg that activate mast cells and basophils to release inflammatory mediators. The direct stimulation of antigen presenting cells (APC) and keratinocytes causes the release of proinflammatory cytokines such as IL-1, TNF-α and IL-12 which increase the influx of T cells into the skin lesions. Superantigens may additionally make T cells unresponsive to topical glucocorticoids (GSs), making patients with AD insensitive to treatment with topical GSs. That is why combined treatment of atopic eczema with a weak glucocorticoid and antibiotic is more effective than treatment with only the potent topical corticosteroid (Schlievert *et al.*, 2008; Na *et al.*, 2012; Orfali *et al.*, 2015).

Other *S. aureus* virulence factors associated with AD. *S. aureus* strains are a source of proinflammatory proteins, *inter alia*, protein A, and have receptors with a high affinity to extracellular matrix proteins such as: collagen (collagen-binding protein, Cn-BP), fibrinogen (fibrinogen-binding protein, Fb-BP), lactoferrin (lactoferrin-binding protein, Lf-BP), and fibronectin (fibronectin-binding protein Fn-BP) (Międzobrodzki *et al.*, 1989; Naidu *et al.*, 1991). IL-4 and IL-13 which are present in the acute phase of eczema due to the increased expression of fibronectin and fibrinogen, enhance the adherence of staphylococci to inflamed skin.

The staphylococcal peptidoglycan induces the production of various cytokines including GM CSF (granulocyte macrophage colony-stimulating factor), a cytokine that is produced in excess in AD (Matsubara *et al.*, 2004).

Other enzymes produced by *S. aureus* also play an important role in the process of infection. Published show that *S. aureus* isolated from AD patients reports exhibits higher proteolytic activity than those isolated from healthy individuals without AD (Międzobrodzki *et al.*, 2002). These enzymes are known to not only cause damage to the skin barrier, facilitating the penetration of allergens and irritants, but can also modify endogenous protease inhibitors, initiate and enhance proinflammatory and allergic responses of the human immunology system and trigger the secretion of IgE by activating Th2 cells. Among the different significant enzymes that are involved in the development of secondary staphylococcal infections in patients with AD, phenol-soluble modulins (PSMs) (Cheung *et al.*, 2014) and the Panton-Valentine leukocidin (PVL) should be mentioned (Cavalcante *et al.*, 2015). These enzymes have the capacity to lyse hosts cells enable *S. aureus* to evade immune response. Moreover, *S. aureus* strains secrete proteins that inhibit chemotaxis (chemotaxis inhibitory protein of staphylococci – CHIPS), impairing the function of neutrophils. The onset and development of the infection also reduces monocyte chemotaxis (Ternowitz and Herlin, 1986; Międzobrodzki and Kaszycki, 2000). The golden carotenoid pigment and superoxide dismutase enzymes also play an important role in staphylococcal infections. These factors, secreted by *S. aureus*, inhibit the production of reactive oxygen species by the host's neutrophils (Międzobrodzki *et al.*, 2008; Krishna and Miller, 2012). Another important virulence factor that contributes to the onset of secondary staphylococcal infections in patients is aureolysin (metalloproteinase). This enzyme inhibits the activity of antimicrobial peptides such as cathelicidins. Furthermore, aureolysin is involved in the activation of other proteases secreted by *S. aureus* mainly serine proteases (Sabat *et al.*, 2008; Foelster Holst *et al.*, 2010). The alpha-toxin has also shown to be an important virulence factor which can quickly induce the release of TNF-alpha, arachidonic acid and platelet activating factor (PAF) from keratinocytes. The toxin forms transmembrane channels that act similarly to calcium channels (Jahreis *et al.*, 2000). Two other staphylococcal proteins

also play an essential role in the pathogenesis of AD, namely NP-taze and p70. These proteins induce the secretion of IL-2 and IFN-gamma from the mononuclear cells isolated from the peripheral blood of patients with AD (Jahreis *et al*., 2000).

Treatment of *S. aureus* infections in AD

In clinical practice, it is essential to properly assess that the onset of the secondary bacterial infection caused by *S. aureus* and to distinguish it from the appearing skin lesions, that have not been affected by AD, and thus justifying the inclusion of antibiotic therapy. Leyden and colleges proposed a quantitative approach to this question after having observed an increased effectiveness of antibiotic treatment of *S. aureus* infections when cell concentrations on the skin were above 10^6 CFU per 1 cm^2 (CFU – colony forming unit). It turns out that quantitative bacteriology is not always possible in a clinical setting, that is why it is recommended to firstly administer antibiotics, after having performed an antibiogram, for a period of 1 to 2 weeks after the appearance of the impetignized skin lesions, and then continue treatment with topical corticosteroids (Leyden *et al*., 1974).

Depending on the severity and extent of the staphylococcal infection, topical antibiotic therapy may be used or general antibiotic treatment is initiated. Affected areas of the skin may be treated by applying topical mupirocin or fusidic acid. Fusidic acid is available only in some European countries, North America and Oceania, excluding the United States. In recent years, more strains resistant to fusidic acid have appeared (fusidic acid-resistant *S. aureus*, FRSA), and so it is advisable to limit its use. Mupirocin is also often used to eradicate *S. aureus* carriage in patients with AD and their family members who are prone to frequent infections. When using this antibiotic it is essential to strictly follow the dosage regimen because there is a risk of placing selective pressure on the strain leading to its resistance to this antibiotic (Petry *et al*., 2012; Gelmetti, 2008).

The treatment regimen recommended for patients with a widespread or severe secondary staphylococcal infection include antibiotics such as erythromycin and next-generation macrolides, *i.e.* azithromycin or clarithromycin. In cases where *S. aureus* strains are resistant to macrolides, the application of penicillinase-resistant penicillins (dicloxacillin, oxacillin, cloxacillin) or next-generation cephalosporins is recommend (Gelmetti, 2008).

A series of studies has also been conducted that report the use of oral antihistamines and topical steroids in the treatment of AD without the use of antibiotics. Results showed that *S. aureus* had been eradicated from the skin in 70% of the patients. In the group of patients where *S. aureus* was not eliminated completely tests revealed an elevated level of IgE and a diminished proliferation of lymphocytes in response to SEB (Guzik *et al*., 2005).

Conclusions

Skin diseases, including atopic dermatitis, are not directly classified as life-threatening diseases. However, the symptoms and burden of the disease cause negative consequences in the lives of patients affected by them. The onset of a secondary infection caused by *S. aureus* in AD patients further increases the patient's burden, complicates and hinders treatment, as well as delays remission. This opportunistic bacterial species has a wide range of virulence factors that significantly exacerbate the disease. Toxins, enzymes and bacterial cell wall components trigger a strong immune response by the patient with a developing secondary infection. Data show that the number of patients with AD is steadily increasing. Finding effective medicines, as well as planning a comprehensive therapeutic strategy aimed both at treating disease symptoms and secondary infections that frequently accompany AD, is considered to be a big challenge both for science and practise. In order to obtain the desired results, it is essential to continue conducting research on both predisposed patients, as well as on the pathogenesis of infections caused by the opportunistic pathogen *S. aureus*.

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