

Bacterial skin colonization and infections in patients with atopic dermatitis *

Colonização bacteriana e infecções da pele em pacientes com dermatite atópica

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Abstract: Atopic Dermatitis is a chronic inflammatory skin disease that affects a large number of children and adults. The disease results from an interaction between genetic predisposition, host environment, skin barrier defects, and immunological factors. A major aggravating factor associated with Atopic Dermatitis is the presence of microorganisms on the patient's skin surface. *Staphylococcus aureus* and *Streptococcus pyogenes*, for instance, can exacerbate chronic skin inflammation. As a result, antimicrobials have often been prescribed to control the acute phase of the disease. However, increased bacterial resistance to antimicrobial agents has made it difficult for dermatologists to prescribe appropriate medication. In the presence of disseminated dermatitis with secondary infection, systemic antibiotics need to be prescribed; however, treatment should be individualized, in an attempt to find the most effective antibiotic with fewer side effects. Also, the medication should be used for as short as possible in order to minimize bacterial resistance.

Keywords: Bacterial growth; Bacterial infections; Dermatitis, atopic; Transformation, bacterial

Resumo: A dermatite atópica é uma doença inflamatória crônica da pele que afeta um grande número de crianças e adultos. A doença resulta da interação entre predisposição genética, fatores ambientais, defeitos da barreira cutânea e fatores imunológicos. Um dos grandes fatores agravantes associados à dermatite atópica é a presença de microorganismos na superfície cutânea desses pacientes. *Staphylococcus aureus* e *Streptococcus pyogenes*, por exemplo, podem exacerbar a inflamação crônica da pele. Como resultado, antimicrobianos são prescritos para controlar a fase aguda da doença. O constante crescimento da resistência bacteriana aos antimicrobianos tem tornado a escolha do mais adequado medicamento uma difícil decisão para os dermatologistas. Na presença de dermatite disseminada com infecção secundária, antibióticos sistêmicos necessitam ser prescritos; no entanto, o tratamento deve ser individualizado, de forma a encontrar o antimicrobiano mais eficaz e com menores efeitos colaterais. Além disso, esse medicamento deve ser utilizado pelo menor tempo possível, a fim de minimizar a resistência bacteriana.

Palavras-chave: Crescimento bacteriano; Dermatite atópica; Infecções bacterianas; Transformação bacteriana

INTRODUCTION

Atopic dermatitis (AD) is a skin manifestation of atopy and a result of hyperreactivity to various antigens. AD occurs in 10% to 20% of children and 1% to 3% of adults, and 40 to 60% of patients also have respiratory allergies.^{1,2,3}

The combination of genetic predisposition, skin barrier dysfunction, and changes in the innate and adaptive immune responses leads to a higher frequency of bacterial and viral skin infections. The innate immune system rapidly mobilizes a non-specific

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first line of defense directed against different pathogens. Defects in this system and dysfunction of the skin barrier culminate in increased allergen penetration through the skin and increased predisposition to skin infections.⁴

In the adaptive response, antimicrobial peptide deficiencies occur, secondary to alterations in T helper 2 cytokines such as interleukins 4 and 13. These alterations are also relevant to the increased predisposition to infections in these patients.⁴

STAPHYLOCOCCUS AUREUS IN ATOPIC DERMATITIS

S. aureus can colonize the skin or the respiratory tract in healthy patients and become pathogenic under conditions such as skin barrier breakdown and diminished immunity.⁵⁻⁷ Nasal carriers and patients colonized by *S. aureus* have been described as a risk factor for the development of infections, and 11% to 43% of the colonized patients acquire active infection through the colonizing agent.⁸

AD patients are even more susceptible to staphylococcal skin infections.⁹ Studies have shown that between 80% and 100% of patients with atopic dermatitis present nasal or skin colonization by *S. aureus*, while the prevalence is 5 to 30% in individuals without AD.⁹ The correlation between eczema severity and colonization with *S. aureus* has already been well documented, and it is generally known that this colonization is an important mechanism involved in the aggravation of the disease in several patients.¹⁰⁻¹²

Recent evidence suggests that production of human antimicrobial peptides, such as defensins and cathelicidins, is decreased in patients with AD, which contributes to greater colonization.⁴ Besides, the skin barrier breakdown that occurs in atopic dermatitis makes it easier for these colonizing bacteria to penetrate through the skin. Changes in the skin of these patients occur due to changes in the regulation of filaggrin and involucrin, lipid deficiency (cholesterol, free fatty acids, ceramides), increased loss of water through the skin, and to greater activity of proteolytic enzymes.^{13,14,15}

The ease with which *S. aureus* colonizes these patients is also explained by the components of the cell wall of the microorganism itself, which have a capacity to induce the production of thymic stromal lymphopoietin by keratinocytes. This cytokine raises the production of CCL17 and CCL20 by macrophages and dendritic cells, and infiltration of Th2 cells and secretion of IL-4 and IL-13 occur, which ultimately favor staphylococcal adhesion to the skin.¹⁶

Colonization by *S. aureus* in atopic dermatitis is linked to the induction of an immune dysfunction with toxicity to keratinocytes and lymphocytic apopto-

sis and to the induction of AD chronicity via lymphocyte stimulation to produce IFN. The products secreted by these bacteria are linked to T cell receptors and provoke their polyclonal activation, besides activating macrophages and antigen-presenting cells and inducing the production of superantigen-specific IgE (functioning as an allergen). This process culminates in the activation of basophils and IgE inflammation, mediated by the production of superantigens. In clinical practice, it was believed that these patients could present erythema and a burning sensation in the lesions, greater severity of the condition, and resistance to steroids; however, a recently published study showed that this association is not really clear.¹⁷

Care of patients with *S. aureus* is important. There are reports of several systemic infections, which include osteomyelitis, endocarditis, and septicemia, that occurred in patients with AD, in whom *S. aureus* was isolated. The species probably came from the skin.¹⁸⁻²⁰ Besides, the *S. aureus* present on these patients' skin may be transmitted to newborns or to other people susceptible to infections caused by these bacteria.¹⁸ A study recently carried out in Brazil did not find a significant association between breastfeeding and *S. aureus* colonization, but there was concordance between colonization in mothers' nasal cavities and their children's skin.²¹

Farajzadeh et al. (2008) analyzed swabs from 50 patients with AD in Iran and found a positive culture in 74% of the patients. *S. aureus* was isolated in 66% of the cases.¹⁹ Bacterial resistance to at least one of the antimicrobials tested was found in 94%. Penicillin resistance was detected in 90% of the patients, erythromycin resistance was found in 66.7%, and resistance to cephalexin was found in 13.8%.

S. aureus has shown a capacity to develop resistance to antimicrobials that were originally active against the species.²² In the early 1940s, *Staphylococcus aureus*, isolated from different infections, presented a good clinical response to penicillin. In 1942, penicillin resistance began to be described in some of these strains, as a result of penicillinase production. From 1944 to 1945, strains with beta-lactamase (penicillinase) production began to be isolated at different hospitals and in different regions, leading to major resistance, which limited the use of penicillin and its derivatives in subsequent years. In 1960, methicillin was launched on the market as a therapeutic alternative to penicillinase-producing strains, since this drug is not affected by this enzyme. However, as soon as in 1961, there were reports of strains that were also methicillin resistant, and they were called methicillin-resistant *Staphylococcus aureus* (MRSA). In 1980, MRSA strains became an endemic problem at different proportions at hospitals in several countries,

including Brazil.²³

Traditionally, infections caused by MRSA were limited to hospitals (HA-MRSA). However, community associated infections or community acquired infections (CA-MRSA) have been increasingly recorded since the last decade. The first report on community-associated MRSA infection in a patient without any contact with the hospital environment was recorded in 1980 in the United States.^{24,25} Subsequent reports on this type of isolates have been described in children and adults worldwide, including Brazil. This indicates the emergence of methicillin-resistant *S. aureus* in the community as a new pathogen.²⁶⁻³⁹ Currently, the possibility of finding clones classified as CA-MRSA in hospitals and HA-MRSA in the community is known, and this makes classification difficult.

Reports on MRSA (Methicillin-resistant *Staphylococcus aureus*) infections in AD patients have been published since 2005.⁴⁰⁻⁴² Some authors suggest that we should suspect CA-MRSA when patients with AD present more intense and generalized erythemas, when the predominant location of infection in these patients is the face, and when these patients present a fetid odor.⁴³ Cross-sectional studies worldwide suggest that the prevalence of MRSA in the population with AD varies from 0 to 30.8%.⁴⁴⁻⁵³ This large variation of prevalence suggests that the real prevalence of MRSA may vary according to the country.

GROUP A BETA-HEMOLYTIC STREPTOCOCCUS AND ATOPIC DERMATITIS

Colonization by streptococcus generally precedes the development of impetiginized lesions (by about 10 days). Group A streptococci often colonize the pharynx of asymptomatic people, especially school-age children.⁵⁴ In cases of infected atopic dermatitis lesions, a high prevalence of co-infection by staphylococci and streptococci was reported, and these bacteria were present in about 70 to 85% of patients.^{55,56}

β -hemolytic streptococci are the main cause of impetigo and erysipelas in humans and are more commonly isolated on the skin of people with AD than on the skin of healthy individuals or of those with other skin diseases.⁵⁷ In patients with poorly controlled AD, the skin barrier is broken and proteins leak from the extracellular matrix. These proteins are important mediators that facilitate adhesion of gram-positive bacteria. Impetigo caused by streptococci progresses fast in these patients, and they often present fever, leukocytosis, and elevated C-reactive protein levels.^{55,56} Characteristically, incidence increases with each outbreak. There is often recurrence after treatment (about 20% within a month), probably due to contact with people colonized in the source environment.⁵⁷ A recent increase in the incidence of impetigo due to

group A streptococci was described in patients with atopic dermatitis in Japan.⁵⁷ This incidence is not known among us.

Streptolysin O, the toxin produced by almost all strains of *S. pyogenes*, in addition to its hemolytic effects, is toxic to other cells, such as polymorphonuclear cells, platelets, and organelles. Serum measurement of the anti-streptolysin O (ASLO) antibody is extremely useful as an indicator of recent streptococcal infection.⁵⁴

S. pyogenes is outstanding among human pathogens for its propensity to cause non-suppurative sequelae. The best documented ones are rheumatic fever and post-streptococcal glomerulonephritis (PSGN). However, skin infections with nephritogenic strains are the main causes of PSGN. There is evidence that treating infections with penicillin can prevent rheumatic fever. However, this does not appear to be the case with PSGN. Thus, the only form of prevention of this major cause of morbidity, especially in children, would be to reduce transmission by treating infected and colonized patients.⁵⁴

Group A streptococci resistance to penicillin has not yet been described, and this is the first-line drug for treatment. However, cases of erythromycin resistance have been described, with implications mainly to the pediatric population and to patients who are allergic to penicillin.⁵⁸ There are no data on bacterial resistance in AD patients in Brazil, and erythromycin, for instance, continues to be prescribed in many places as a first-line drug for patients with infected AD skin lesions due to its low cost and availability in the public health system.

TOPICAL ANTIMICROBIALS AND ANTISEPTICS

Fusidic acid is an antibiotic that is only available in some countries of Europe, America (including Brazil) and Oceania, but not in the United States.⁵⁹ It is commonly used as an anti-staphylococcal drug and is one of the first line medications to treat impetigo.⁶⁰ However, in the last decade, clones of *S. aureus* associated with impetigo appeared and were disseminated; they were resistant to fusidic acid (FRSA).⁶¹ The disseminated and inadequate use of its topical presentation in chronic dermatoses, such as atopic dermatitis, has been considered responsible for this, and specialists have recommended restricting or even abolishing the topical use of fusidic acid in several countries.⁶² Despite this, studies in patients with secondarily infected atopic dermatitis showed that the rates of resistance in this population remain low.⁶³ In a study carried out at an outpatient clinic in England, resistance of isolated *S. aureus* to fusidic acid and methicillin clearly increased with the age of the children when groups aged 12 months, 1 to 5 years, and over 5 years

old were compared.⁶⁵

Mupirocin is an antibiotic commonly used to treat skin infections and to eradicate nasal colonization of *S. aureus*, including MRSA. However, the criteria for this practice have been questioned, due to reports on growing rates of resistance.^{59,64} In Brazil, until a few months ago, products containing fusidic acid and mupirocin were usually sold without any restrictions at chemists. However, after a recent resolution by ANVISA (the Brazilian National Health Surveillance Agency), they started to be sold only by prescription, like all antimicrobial drugs.⁶⁵

Topical use of gentamycin in association with corticosteroids is common in commercial products. Its activity against gram-positive bacteria, such as staphylococci, made it popular for use in infected dermatites.^{59,63}

Retapamulin is a new topical antimicrobial described for use in pyodermites.⁶⁶ In a recent study, retapamulin was active in vitro against clinical isolates of MRSA and *S. pyogenes* collected from adult and pediatric patients with skin infections in six European countries, including isolates resistant to other inhibitors of protein synthesis and other multi-resistant isolates.⁶⁷ There are no specific studies in patients with atopic dermatitis, but retapamulin appears to be a safe, effective alternative to treat superficial infections in these patients.⁶⁸

Topical antiseptics such as triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether) or chlorhexidine present a low rate of resistance and may be used in emollients. Topical use of triclosan has proved effective in significantly reducing skin colonization by *S. aureus*.⁶⁸ Furthermore, patients with AD do not appear to be at a significantly greater risk of sensitization by topical antimicrobials and antiseptics.⁶⁹

For children up to the age of 3 months, sodium hypochlorite may be added to bathwater in order to reduce *S. aureus* colonization. A recent study with 31 children compared anti-staphylococcal measures (nasal mupirocin and sodium hypochlorite added to bathwater) with placebo (nasal vehicle and bath without additives). The study showed a great reduction in EASI score in the mupirocin/hypochlorite group at the end of one and three months. However, the difference in baseline scores (higher in the treatment group) may have been biased and compromised the results. Furthermore, the possibility of sites of crusted or eroded dermatitis triggered by the use of hypochlorite cannot be excluded.⁶⁸

SYSTEMIC ANTIMICROBIALS

Systemic treatment with antibiotics plays an important role in managing atopic dermatitis during exacerbations in the presence of a secondary infec-

tion.⁷⁰ Prophylactic treatment only increases resistant rates and has no benefit in the course of the disease.

Treatment with first and second generation cephalosporins for 7 to 10 days is recommended for infections with *S. aureus*. The dose of Cephalexin is 50-100mg/kg/day four times a day and the dose of Cefadroxil is 25-50mg/kg/day twice a day. Cefaclor is used in doses of 10-40mg/kg/day thrice a day. Macrolides and Clindamycin can also be used as alternatives, especially in patients allergic to penicillin. The recommended dose of Erythromycin is 30-50mg/kg/day four times a day for 7 to 10 days and the dose of Azithromycin is 10mg/kg/day in a single daily dose for 3 to 5 days. Clindamycin should be used at a dose of 40mg/kg/day taken for 3 to 7 days.^{71,72}

Treatment of infections with *Streptococcus pyogenes* in patients with atopic dermatitis is done with Amoxicillin/clavulanate in doses of 25mg/kg/day for 7 to 10 days or with Clindamycin in doses of 40mg/kg/day taken for 3 to 7 days, although gastrointestinal discomfort may limit their use. First or second generation cephalosporins may be more appropriate for these patients. The recommended doses are the same used for treatment of staphylococcal infections.⁷³

Treatment for patients with recurrent secondary infection who use many courses of antibiotics to remain in remission takes longer. Because of concerns about microbial resistance, Sulfamethoxazole/trimethoprim is the antibiotic of choice for long term use.⁷³

The most common adverse effects of cephalosporins include gastrointestinal disorders such as nausea, vomiting, diarrhea and pseudomembranous colitis. Skin eruptions, including urticaria, maculopapular eruptions and pruritus are observed in 1-3% of patients. Five to 10% of patients allergic to penicillin are also allergic to cephalosporins. Cephalosporins should be avoided in patients with a history of type I or IV hypersensitivity to penicillin. Hemolytic anemia rarely develops, and eosinophilia and neutropenia are observed sporadically. Clindamycin can cause colitis, diarrhea, nausea, vomiting, and abdominal pain. Cutaneous hypersensitivity reactions, pruritus, jaundice, and elevated transaminases and alkaline phosphatase may develop. Neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia are rarely seen. The adverse effects of Amoxicillin/clavulanate include diarrhea, nausea, vomiting, and allergic reactions (rash; hives; itching; dyspnea; edema of the mouth, face, lips, or tongue). The most common side effects of Sulfamethoxazole/trimethoprim are skin rashes and gastrointestinal disturbances. Allergic reactions may occur in patients who are hypersensitive to the drug (e.g. fever, angioneurotic edema, anaphylactoid reactions, hypersensitivity reactions and serum sickness).⁷⁴

CONCLUSIONS

In colonized patients with atopic dermatitis, the density of *S. aureus* in skin lesions tends to increase according to disease severity, and it was suggested that *S. aureus* could promote inflammation due to the action of superantigens.^{43,75} The theoretical interpretation according to which reduction of colonization by *S. aureus* could lead to clinical benefits helped disseminate the use of antimicrobials and anti-staphylococcal interventions in treating non-infected eczema.

The use of oral antimicrobials to treat non-infected eczema was not associated with improvement of the dermatitis.⁷⁶ There is also evidence that the skin is rapidly recolonized when the antimicrobial treatment ceases.⁴⁶ Studies using topical antibiotics associated with corticosteroids also failed to show benefits compared to the use of corticosteroids alone.^{63,77}

Current concepts about the role of secondary infections in atopic dermatitis suggest that they act as a trigger when atopic dermatitis becomes worse.

Indeed, superantigens and staphylococcal and streptococcal toxins can trigger the activation of T cells, induce IgE-mediated degranulation of mastocytes and basophils, and activate inflammatory cells. The use of topical antiseptics such as chlorhexidine, triclosan, and hypochlorite is an option to control staphylococcal flora, but may cause skin irritation.

Antimicrobials in AD should be used with caution to reduce the incidence of bacterial resistance. Topical antimicrobials can be used in localized infections. Mupirocin can be used for decolonization, but at the expense of increased levels of bacterial resistance. In extensive dermatitis with secondary infection, the use of systemic antimicrobials is essential, but treatment should be customized, seeking to choose the most effective agent with fewer side effects to be used for as short as possible, minimizing the potential for resistance induction. The use of systemic antimicrobials for decolonization by *S. aureus* is not recommended. □

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