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ASSOCIATION BETWEEN BACTERIAL INFECTION AND SEVERITY OF ATOPIC DERMATITIS

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory and residing skin disease. Several factors are known to promote bacterial colonization in AD skin, such as altered epidermal barrier, increased bacterial adhesion, defective bacterial clearance, and decreased innate immune responses. Compared to normal individuals, people with AD exhibit higher skin bacterial density. It is found that infection in AD skin associates with the increased severity of inflammation, which was shown by the SCORAD index. Incidence of skin infection was also found higher in more severe AD. Clinical manifestations, especially severity and intensity of lesion, showed association with the incidence of infection, suggesting its role as predicting factors and potentially serve as a basis in giving antibacterial treatment in AD.

Introduction

Atopic dermatitis (AD), also known as eczema, is a chronic inflammatory skin disease. This condition resides as the atopic march begins which would develop as food allergy in infants and bigger child, allergic rhinitis in school-age children, as well as asthma in older child, teenagers and young adults.[1] According to The International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence of AD varied between 0.3 to 20.5% within 56 countries. Study Group of Child Dermatology reported 23.67% of children in Indonesia had AD, and was being the most frequent skin disease found in the country.[2]

Children with AD were found to be more susceptible to skin infection. Likewise, having skin infection was also found to worsen the manifestations of AD. In AD, the skin structure differs with non-AD skin. The low level of lipid found in AD causes changes in skin barrier, which includes higher transepidermal water loss (TEWL). This high water loss favors colonization of microorganisms in areas where AD develops. Invading microorganisms include bacteria, virus or fungi. The most frequent pathogen found was *Staphylococcus aureus,* responsible in 90% of skin infection in AD persons, vs 5% in non-AD persons. Infection in AD person was also known to induce immune system which promotes inflamation thus intensifies preexisting AD.[5]

Atopic Dermatits

Atopic dermatitis is a chronic inflammatory skin disease. Typical skin findings involve erythematous lesions with irregular borders, edema, vesicles and exudate in acute phase or skin thickening (lichenification) in chronic phase. AD often associates with higher level of serum IgE, family history of atopic disease as well as other atopic conditions such as allergic rhinitis, allergic conjunctivitis, or asthma.[6]

The prevalence of children with AD was 10-20% worldwide. According to the International Study of Asthma dan Allergies in Childhood (ISAAC) conducted in 2013, the prevalence rate tends to increase especially in 6-7 year olds in developing countries and low income countries such as Latin America and South East Asia.[3]
In terms of patophysiology, the main theory skin lesion development in AD is the disruption of skin barrier. This theory involves genetic defect in fillagrin, the type of protein essential in maintaing epidermal structure. As a consequence, dermal immune cells interacts with external antigen causing allergic cascade within skin layers. Inflammatory mediators and cytokines release triggers itching which often followed by skin scratching. This action of scratching further deteriorates epidermal structure and promotes transepidermal water loss as well as favoring invasion of pathogens. This cycle is also known as the itch-scratch cycle. In AD individual, an imbalance between Th1 and Th2 activities is observed, in which antigen (allergen) induces Th2 cells causing IL-4 release.[7-10]

Clinical manifestations of AD are divided into four sub-types according to age group. Infantile AD begins to appear in two months-olds showing lesions that mimic spoiled milk appearance on cheeks and chins, that is erythematous plaque, fine papulo-vesicles, that might develop into crust due to scratching. In bigger children age 1-4 years, lesions typically found on flexures and extensor sides of extremities, perioral, around eye lid, hands and neck. In older children (4-16 years old) dermatitis appeared symmetrically on flexures of upper and lower extremities. In adult form, AD appeared less specific, which might involve facial skin, upper body, lip flexures or hands. Inflammatory lesions are normally dry in appearance, with flattened papules, lichenification plaque, minimal squamous flakes, often with excoriation and exudation due to scratching.[11] Diagnosis of AD commonly utilizes clinical criteria such as Hanifin and Rajka criteria, involving 4 major criteria and 23 minor criteria. Typical AD diagnosis is made in individual presenting with 3 major criteria and 3 minor criteria.[12]

Atopic Dermatitis Scoring

One tool to identify the degree of inflammation in AD persons is SCOring Atopic Dermatitis (SCORAD). This scoring system was developed by The European Task Force on Atopic Dermatitis, can be used clinically to determine the severity of AD.[6] To calculate the SCORAD, the following formula is used:[12]

$$SCORAD = A/5 + 7B/2 + C$$

In which A is the sum of skin surface showing AD lesions according to the rule of nine; B is the sum score of 6 inflamation characteristics such as erythem, edema/papules/blistering vesicles, oozing/crusted, excoriated, lichenification/scaly, or dry skin (where 0 being absent, 1 being mild, 2 being moderate, and 3 being severe); and C is the sum score of itching and sleep disturbance (with the scale of 0-10).

Based on the SCORAD score system, mild AD is characterized by SCORAD score < 25, in which the symptoms are mild with no seondary infection. Moderate AD shows SCORAD score of 25-50, typically involve lichenification and sleep disruption. Wheras severe AD is determined by SCORAD score of > 50, where severe erythem, itching, lichenification, sleep disturbance as well as secondary infection are found.[12]

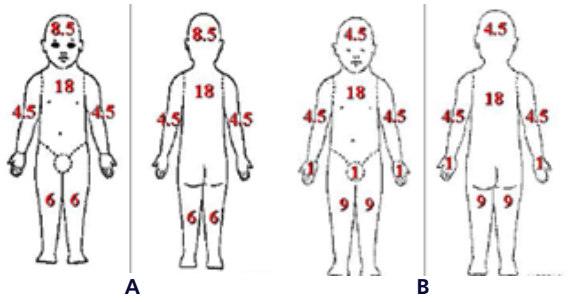

Figure 1: A. The Rule of nine for children below 2 years-old; B. The Rule of nine for children 2 years and older

Normal skin flora

Skin is a part of the human body that constantly in contact with external environment making it susceptible for transient microorganisms invasion. Nonetheless, normal microorganisms (flora) of the skin also exist that resides accordingly to the anatomical locations. Predominant normal flora includes aerob bacteria or anaerob dyphteroid basil (such as *Corynebacterium*, *Propionibacterium*, spesies *Micrococcus, Taphylococcus*); aerob and anaerob nonhemolytic *Staphylococci* (such as *Staphylococcus epidermidis, Staphylococcus aureus* in small amount, and *Peptostreptococcus sp*); gram positive, aerob, spore producing bacile commonly found in water, air, or soil; *Streptococcus alfa hemoliticus* (*Streptococcus viridans*); and gram negative coliform bacile, or *Acinetobacter*. Fungi and yeast normally resides on skinfold whilst acid-resistant microbacteria typically inhabit areas where sebaceous secretion is prominent such as genitals and external ear canal.[13]

A number of factors are known to cause multiplication of this resident skin flora. External factors include climate or skin blockage. Whereas, internal factors involve preexisting conditions such as diabetes mellitus or medication use. Superficial microorganisms can be controlled using soap containing hexachlorophene or other disinfectants, however those flora would re-grow as sebaceous activity occurs as well as sweating, even when the environmental exposure to skin is absent.[14]

Infection in AD lesions

Several microorganisms namely bacteria, virus, or fungi are thought to cause infection in AD lesions. *Staphylococcus aureus* was found in 75-100% of AD lesions, vs 30-100% in non-lesion skin. *Staphylococcus aureus* is positive catalase and negative oxidase which capable of producing coagulase enzyme. This species ferments glucose and manitol leading to formation of lactic acid. In medium culture, it forms yellowish big colony and displays hemolytic feature in blood medium.[5,13]

One study conducted in China reported etiology of infection in AD skin included *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus haemolytic*, *Staphylococcus lugdunensis*, *S. capitis*, *E. coli*, *Micrococcus tetragenus*, *Enterobacter cloacae*, *Proteus sp*. Clinical manifestations of the infection showed erythema, regular borders, crusting, pustules, fever and lymphadenopathy.[15]

Viral infection in AD lesions developed due to sellular immune dysfunction. Additionally, immunosupressant agent used in controlling AD favors viral invasion. Viral species commonly found in AD infection includes *Herpes Simplex Virus type-1(HSV-1), Human Papilloma Virus, Coxsackie Virus, Vacinia Virus*, dan *Molluscum contagiosum.*[14]

Other microorganism such as fungi are also known to cause infection in AD lesions that includes *Malassezia* or *Pityrosporum*. In this type of infection, lesions frequently appear in the form of AD on head and neck, as well as seborrhoic dermatitis. Furthermore, infections due to *Candida albicans* and dermatophyte (such as *Trichophyton* and *Epidermophyton*) were also reported.[16]

Association between bacterial infection with the severity of AD

Staphylococcus aureus is the most commonly found bacteria causing infection in AD skin (90% vs 5% in persons without AD). Bacterial density is also 100-1000 times higher in AD skin compared to non-AD skin. A number of factors are known to promote bacterial colonization of *Staphylococcus aureus* in AD skin such as disruption of skin barrier, increased in bacterial adhesion, pathogen clearance, and dysfunction in innate immune response. *Staphylococcus aureus* is a potent corneocyte invader that is capable to penetrate epidermis intracellularly. This occurs as the AD skin typically lacks lipid layer. In AD, the skin pH is usually slightly more alkaline and has less sphingosine in the stratum korneum of both lesion and non-lesion skin. AD skin is commonly dry due to water loss in transepidermal layer as the lipid structure changes.[5]

In AD skin, the adhesion to *Staphylococcus aureus* is more forceful due to atopic inflammation on the skin. *Staphylococcus aureus* penetrates through defect in skin layers caused by inflammation or scratching. *Staphylococcus aureus* produces a group of toxin called superantigen that interacts with antigen presenting cells such as macrophages and dendritic cells. Following bacterial capture, dendritic cells cleave the antigen into smaller peptides. These peptides bind to major histocompatibility complex (MHC) class II molecules and are expressed on the surface of the dendritic cells. These peptide-MHC II bindings will be recognized by naive T-CD4$^+$lymphocytes (Th0 cell).

The T-CD4$^+$ cells are subdivided into two classes based on the cytokines released, the Th1 and Th2 cells. Th1 cells produce interleukin-2 (IL-2) and interferon- (IFN-), whilst Th2 cells produce IL-4, IL-5, IL-6, IL-10, and IL-13. In atopic individuals, Th0 cells tend to proliferate into Th2, thus IL-4 and IFN- more prominent. The IL-4 and IL-13 released by Th2 binds with its receptors, the IL-4R and IL-13R, on the surface of B cells. This cascade activates isotype switching especially the IgE-class-switching-recombination within DNA sequence in B cells' nucleus, leading to specific IgE molecule formation towards superantigen. Basophils in this individual de-granulates, causing histamine release that triggers itch-scratch cycle as well as causes inflammation on AD skin.[5,10]

The severity of AD is known to associate with *Staphylococcus aureus* growth. It can be shown using scoring tool named SCORAD that assess the severity of AD. A study conducted in China in 2015 investigated 94 AD patients based on SCORAD that included 4 mild, 56 moderate and 35 severe AD. The study found the *Staphylococcus aureus* growth is associated with SCORAD ($p < 0.004$) and lesions severity including skin erytema ($p = 0.0022$) and lichenification (p 0.035). Severe AD lesions also showed higher risk (2.16 fold) of developing *staphylococcus aureus* infection.[17]

Infection in AD skin was found to eventually worsen the inflammation caused by AD. It showed linear association with the degree of AD, being most frequently found in severe AD. Previous evidences showed the incidence of skin infection increases as the severity of AD intensifies. The incidence of infection was 15-50% in mild AD, 52-78% in moderate AD, and 77.5-100% in severe AD. [8-20] On contrary to previous findings, one study found gram positive bacteria do not associate with the severity of AD. This is thought to be due to the fact that only gram positive infection was assesed, excluding gram negative infection that might lead to narrow applicabilty.[14]

It is also found that clinical manifestations especially severity and intensity of the lesions, might have predictive value in *Staphylococcus aureus* colonization or infection in AD persons. Thus it may also serves as a supporting data in treating AD patients prior to bacteriologic study results. It is also advised to conduct skin culture not only in children with chronic and extensive AD, but also in those experiencing worsening of AD manifestations.[17]

Summary

Atopic dermatitis condition causes changes in skin layers favoring pathogen invasion. Such changes include skin barrier defect, more alkaline skin pH, and lack of lipid deposit increasing transepidermal water loss. Invading pathogen in AD infection can be bacteria,

virus, or fungi, with *Staphylococcus aureus* being the most commonly found infection in AD skin. The infection on AD skin also known to worsen pre-existing inflammation in AD individuals.

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