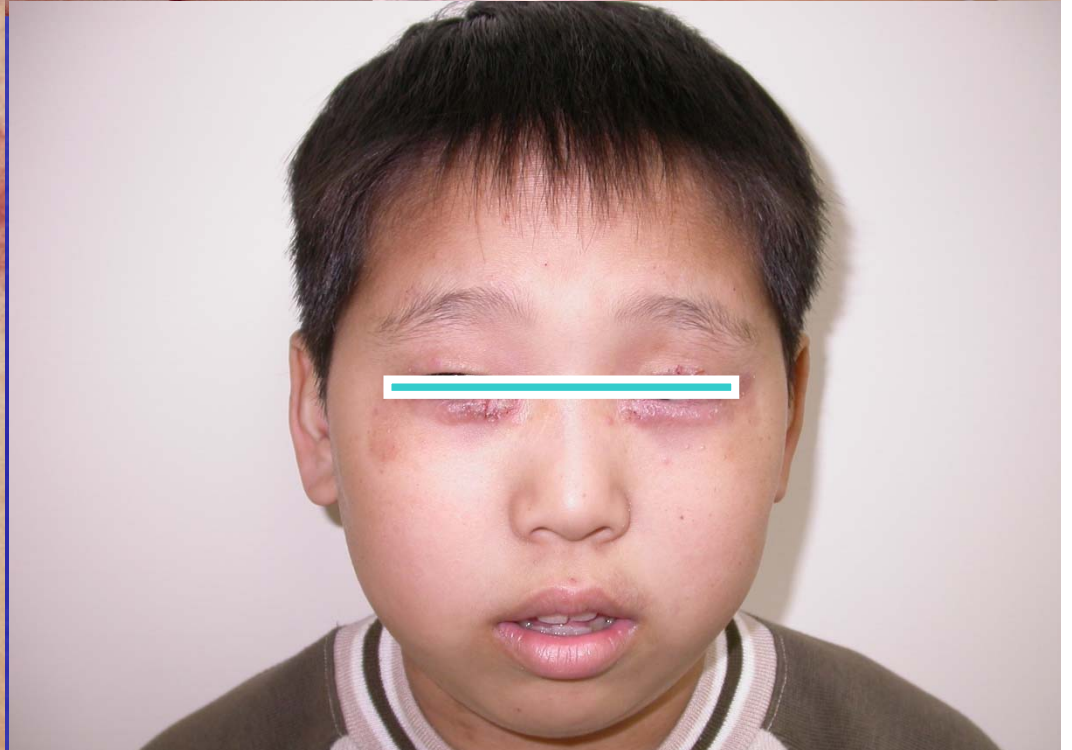


Atopic Dermatitis

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Introduction

- A chronic inflammatory skin disease associated with cutaneous hyperreactivity to environmental triggers
- influenced by bacterial factors, particularly *Staphylococcus aureus*
- *S. aureus* colonization on the skin of patients is approximately 90%-100%
- Up to 65% produces exotoxins with superantigenic properties
- Predates the development of asthma and/or allergic rhinoconjunctivitis

Allergy. 2003 Mar;58(3):252-6

Br J Dermatol. 2002 Jul;147(1):55-61

Introduction

- Clinical features are age related
- A new subgroup (suffer from AD for the first time at adult age)
- Patch Test is still experimental
- Double-blind placebo-controlled food challenge (the gold standard, 10% are not IgE-mediated)

Pathogenesis

- Unclear, Multifactorial
- prevalence is rising in the industrialized countries
Curr Opin Pediatr. 2002 Aug;14(4):410-3.
- Staphylococcus aureus
- Genetic and pre- and perinatal influences
(Black and Asian race/ethnicity, male gender, higher gestational age at birth, and maternal history of atopy)
Pediatrics. 2004 Mar;113(3 Pt 1):468-74
- Protective effect is established independently early in life
BMJ. 2004 May 22;328(7450):1223. Epub 2004 Apr 30
- Food allergens (<5y) and aeroallergens (7-12y)

Pathogenesis

- High IgE and early sensitization (1 yr)
- Decrease INF- γ in intractable AD
Int Arch Allergy Immunol 2004 Jun;134(3):240-247
- Product of interactions between susceptibility genes, the environment, defective skin barrier function, and immunologic responses
J Clin Invest. 2004 Mar;113(5):651-7.
- skin development is not complete at birth
Pediatr Dermatol. 2002 May-Jun;19(3):256-62.

Skin barrier function

- Stratum corneum, keratinocytes, immune cells, and nerve fibers are in close proximity to one another and induce itch.
- Impaired barrier function associated with the itch-scratch cycle further augments this vicious cycle
- Drives downstream inflammation and allows unrestricted antigen access

Curr Allergy Asthma Rep. 2008 Jul;8(4):306-11

Skin barrier function

- Loss of function mutations in barrier protein filaggrin and diminished expression of antimicrobial peptides
J Allergy Clin Immunol. 2008 Dec;(122(6):1074-81
- Th2 cytokines can influence the expression of filaggrin and antimicrobial peptides
Clin Exp Allergy.2009 Mar;39(3):310-6

complications



Eczema herpeticum

usually primary HSV infection



terial infection

ureus colonization : >90%

emolytic group A *Streptococcus*

D vs Staphylococcus aureus (SA)

SA and GAS (3-6y, 53%) were isolated from all body sites

Enteric G(-) and bacteroides were often in buttock and leg

J Med Microbiol. 2002 Oct;51(10):808-12

Antibacterials and topical corticosteroids therapy produces a more rapid decrease in SA colonization but not clinical improvement of dermatitis

Am J Clin Dermatol. 2000 Jul-Aug;1(4):211-5

D vs Staphylococcus aureus (SA)

An exacerbation factor, cause of relapse or worsening of AD

Often coexisted with beta-hemolytic streptococci (50%). (CNSA?)

Int J Tissue React. 2003;25(2):47-50

Skin of patients with AD has increased avidity for binding to SA and deficient to generate antimicrobial peptides

Curr opin Pediatr. 2003 Aug;15(4):300-404

D vs Staphylococcus aureus (SA)

SEA and SEB contribute to AD by humoral immunity thro IgE production as a superantigen (SsAg)

Exfoliative toxin x may exacerbate AD, particularly in infants, not thro specific IgE

Clin Exp Allergy. 2004 Jun;34(6):984-93

Hypogammaglobulinemia G is part of an immunologic impairment of AD which favours the susceptibility to secondary infection

Ann Allergy. 1989 Aug;63(2):121-6

AD vs Staphylococcus aureus (SA)

High positive rates of SEA/SEB-specific IgE
Ab--- value for evaluating

Pediatr Int. 2004 Jun;46(3):337-41

AD have increase number of Treg cells
with normal immunosuppressive activity—

--SsAg reduces immunosuppressive
activity of Treg--- augment T-cell
activation

J Allergy Clin Immunol. 2004 Apr;113(4):756-63

D vs Staphylococcus aureus (SA)

SEB induced production of Th2 cytokine and up-regulation of CCR4+ cells in AD

SEB-reactive CD4+ T cells from AD patients were more resistant to SEB-induced apoptosis

J Immunol. 2003 Jul 15;171(2):1102-8

AD had higher levels of serum SEB-specific IgG, IgM and IgE.

SBE-IgE correlated with the severity of AD

Allergy Asthma Proc. 2003 Jan-Feb;24;(1):67-71

D vs Staphylococcus aureus (SA)

Human skin contains antimicrobial peptides, cathelicidins (LL-37) and beta-defensins (HBD-2)

Immunostaining for these peptides was significantly decreased in acute and chronic lesions from patients of AD (immunodot blot analysis, western blot analysis)

D vs Staphylococcus aureus (SA)

Lipoteichoic acid from SA enhances allergen-specific IgE by a mechanism thro up-regulation of CD40L-expression Th cells

Clin Exp Allergy. 2003 Jun;33(6):842-8

SA exotoxins inhibit eosinophil apoptosis, increased surface Ags expression, and enhanced cytokine-activated oxidative burst--- triggered allergic inflammatory reactions

J Allergy Clin Immunol. 2002 Mar;109(3):477-84

D vs Staphylococcus aureus (SA)

Macrolide abx inhibited SEB-induced mRNA expression of IL-4 and IL-5 in PBMCs from patients with AD.

Also suppressed lipoteichoic acid-induced or peptidoglycan-induced IL-5 mRNA expression

J Interferon Cytokine Res. 2004 Mar;24(3):197-201

In transgenic mice, cutaneous application of Cowan 1 strain of SA increased serum levels of IL-18 and IgE

Int Immunol. 2003 May;15(5):611-21

D vs Staphylococcus aureus (SA)

In NC/Nga mice (model of AD), Cefarithromycin reduced degranulated mast cells and MHC class II-positive cells— antibacterial and immunological effects

Chemotherapy. 2003 Sep;49(5):222-8

Secondary infection: an alteration of the skin barrier and inflammation of the upper dermis.

Bacteria (SA & GAS), fungi (malassaezia spp), viruses (HSP)

Am J Clin Dermatol. 2003;4(9):641-54

The Impact of Food & Aeroallergens in AD

Food allergens play a major role in the exacerbation and maintenance of eczematous lesion

Cow's milk, hen egg, wheat and soy--- infants

Nuts, fruit , vegetable--- adolescents

Food specific T cells--- adult

RAST (sp 42%-64%), SPT (44%-53%),

APT (69%-92%) are poor reliability

DBPCFC is the gold standard in diagnosis

The Impact of Food & Aeroallergens in AD

A diary for food consumption

Specific IgE to milk, egg, fish and peanut—95% predictive positive value

Allerg Immunol (paris). 2002 Sep;34(7):241-4

2/3 intolerant to food proteins have NO evidence of IgE sensitization to relevant food protein

Allerg Immunol (paris). 2002 Mar;34(3):95-7

The Impact of Food & Aeroallergens in AD

Food allergy is regarded as IgE mediated
BUT some children with food allergy IgE hypersensitivity cannot be proven.

10% of positive DBPCFC results are not IgE mediated

Wheat--- often non-IgE-sensitized

Hen's egg--- often in sensitized group

The Impact of Food & Aeroallergens in AD

Severe AD had higher IgE serum levels
0-3 yr--- SPT positive to food allergens
with high IgE and severe AD symptoms---
high risk of allergic resp diseases

Pediatr Dermatol. 2000 Jul-Aug;17(4):261-5

Contact with food allergen must also be
avoided by: skin (cosmetic), respiratory
tract and drug intake.

Allerg Immunol (paris). 2001 Nov;33(9):351-6

The Impact of Food & Aeroallergens in AD

Allergens applied epicutaneously can influence the systemic allergic response

Children with AD and positive skin test have more severe asthma

Epicutaneous exposure to Ag in AD enhance the development of asthma

Systemic immune activation in AD is supported by increased Th2 cells, eosinophils, macrophages, and IgE.

The Impact of Food & Aeroallergens in AD

Patients with AD present aeroallergen-specific T-cell responses associated with worsening of symptoms when exposed to specific aeroallergens

Exposure to high conc. of mite in early infancy may develop AD during the first 3 years of life.

Allergy. 2004 Aug;59 Suppl 78:53-60

The Impact of Food & Aeroallergens in AD

Aeroallergens induce a positive APT in about 50% of patients with AD

J Allergy Clin Immunol. 2000 may;105(5):1008-16

Damage of the skin barrier function enhance epicutaneous sensitization to aeroallergens

J Allergy Clin Immunol. 1999 Dec;104(6):1280-4

Dust mite (42.8-65%) and cockroach (25.7-35.9%) were the commonest allergens

Thorax. 1994 Dec;49(12):1205-10

treatment

Avoid exposure of food and aeroallergens?

Only pure amino acid mixtures are considered to be nonallergenic (hypoallergenic formula— extensively or partially)

Exclusive breastfeeding for 4-6 months

BF is not a risk for developing AD, it is protective when compared with conventional cow's milk

Allergy. 2004 Aug;59 Suppl 78:45-52.

Avoidance of allergenic foods during pregnancy or the use of hydrolyzed or soy formula does not prevent eczema

Delayed introduction of solids may decrease with eczema

treatment

Systemic antibacterials in combination
with topical corticosteroid--- large areas

Topical abx plus topical corticosteroid---
small area

Gentian violet not only reduces SA
dramatically, but also reduces the severity
of the eczema

Dermatology. 1999;199(3):231-6

reatment

Cyclosporin A (CsA):

2.5-5 mg/Kg orally X 8wks, improved clinical symptoms in children suffering from severe AD

Pediatr Allergy Immunol. 2003 Feb;14(1):559

2.8mg/Kg/D X 6mo, rapid relief but NOT long-lasting and relapse (3mo)

Vitamin B(12) cream:

an effective scavenger of nitric oxide, a new therapeutic approach

NO synthase inhibitor, N omega-nitro-L-arginine, led to a clear decrease in pruritus and erythema in atopic dermatitis.

Br J Dermatol. 2004 May;150(5):977-83.

treatment--- antihistamine

Mast cells and histamine points

There is conflicting evidence for increased mast cells and histamine in AD lesions, but most studies that showed an increase were not controlled.

Studies of psoriasis, lichen planus, and other chronic inflammatory skin conditions showed similarly increased mast cell numbers, suggesting that these are nonspecific inflammatory accompaniments.

The direct histamine role in eczematization and AD pathogenesis remains speculative.

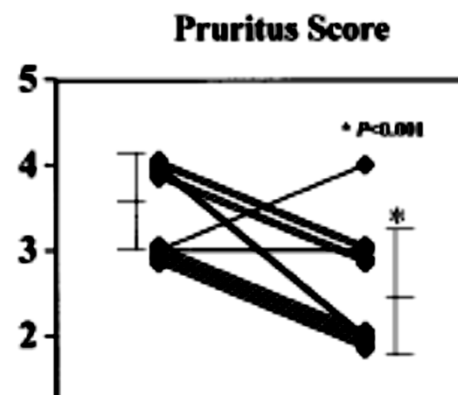
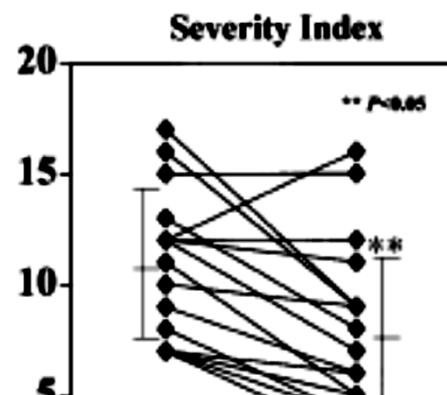
Manifin JM. [1992] Do mast cells play a role in atopic dermatitis? In: Kaliner M, Metcalfe D, editors. The mast cell in health and disease. New York: Marcel Dekker; 1992. p. 629-51.

treatment

antihistamine

Effective treatment of pruritus in atopic dermatitis using H₁ antihistamines (second-generation antihistamines): changes in blood histamine and tryptase levels

Akiko Imaizumi, Tamihiro Kawakami*, Fumiko Murakami, Yoshinao Soma, Masako Mizoguchi



Topical corticosteroids

Key points

Topical steroids continue to be the mainstay of therapy, although there is a paucity of data that examine the effects of prolonged topical steroid use on the growth curve and bone-density in children.

An effective general strategy to skin management is as follows:

- Step 1. Induction of remission
- Step 2. Stabilization and maintenance
- Step 3. Rescue of flares

Rapid flares of AD are best treated with 5 to 7 days of a medium- to high-potency topical corticosteroid ointment. The goal of this approach is to induce partial remission of disease activity. Safer long-term topical maintenance strategies then must follow this induction phase.

Neuroendocrine-Pituitary-Adrenal Function and Glucocorticoid Sensitivity in Atopic Dermatitis

PEDIATRICS Vol. 105 No. 4 April 2000

Suppression was rarely found in children or adolescents
with moderate to severe AD who used
low or moderately potent topical GCs over many years

treatment

Tarcolimus & Pimercolimus:

Inhibit proinflammatory cytokine production in cutaneous lymphocytes

reduced expression of the high-affinity IgE receptor FcεRI, a reduced stimulatory capacity of lesional DCs, but not DC apoptosis

J Allergy Clin Immunol 2004 Jul;114(1):137-43

Reduces all steroid-induced effects

Did not increase the risk of skin infection

Herpes infection (face and neck), 2.8% to 4.7%

J Dermatol 2004 Apr;31(4):277-83

treatment

Used when topical corticosteroid (TCS) fail and in patient ≥ 2 yrs

Whether it is effective after topical TCS failure

No more effective than a class II TCS

Burning and pruritus at the site of application (5%)

treatment

- 1. Severely skin infection and skin cancer maybe the serious side effect
- 2. Drugs interaction
- 3. No reason to use Tacrolimus, at least pending studies showing it is effective after TCS failure

calcineurin inhibitors

	Tacrolimus (Protopic)	Pimecrolimus (Elidel)
e	ointment	cream
culitis	common	uncommon
ct	immunosuppression	Anti-inflammation
ivalent	Rinderon / Cutivate	Stronger than 1% hydrocortisone

Treatment for Pediatric AD

Tubifast



Wet wraps therapy (WWT)

Useful in secondary care for inducing remission

Not a treatment for mild eczema

Should not be use long term

Clin Exp Dermatol. 2008 Nov;33(6):685-8

Suffered more skin infections requiring antibiotics.

Arch Dis Child.2006 Feb;91(2):164-8

Wet wraps therapy (WWT)

Conventional therapy with hydrocortisone and emollients alone is as effective as WWT for moderately severe, AD

Clin Exp Dermatol. 2004 Jul;29(4):348-53

1/10 diluted 0.1% mometasone furate oint. Plus
1/10 diluted 0.005% fluticasone propionate oint.
followed with WWT are improving refractory AD

Pediatr Dermatol. 2001 Jul-Aug;18(4):343-8

Probiotics for atopic dermatitis

More convincing for prevention than
treatment

*J Allergy Clin Immunol.*2008 Jan;121(1):116-121

Reduced cumulative prevalence of eczema
but not atopy

*J Allergy Clin Immunol.*2008 Oct;122(4):788-94

Prognosis

- 65% improving
- mild cases >50% exacerbation
- moderate cases 77-91% --- life-long affected
- 18%- 40% spontaneously recover



Thank you
for
your attention!

謝謝！