

confounders include increased exposure to tobacco smoke and increased respiratory symptoms before the study in the children randomly assigned to the probiotic group. Additional studies are required to assess probiotic use in children with a personal or family history of atopic disease.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2011-2107AAAA

Karla L. Davis, MD
Fort Leavenworth, KS

The Efficacy and Safety of a Chinese Herbal Product (Xiao-Feng-San) for the Treatment of Refractory Atopic Dermatitis: A Randomized, Double-Blind, Placebo-Controlled Trial

Cheng HM, Chiang LC, Jan YM, Chen GW, Li TC.
Int Arch Allergy Immunol. 2011;155(2):141-148

PURPOSE OF THE STUDY. To determine if the Chinese herbal product Xiao-Feng-San (XFS) taken orally could significantly improve symptoms of severe intractable atopic dermatitis.

STUDY POPULATION. A total of 71 Taiwanese subjects (age range: 8.4-22.6 years [median: 13.1 years]) with history of severe, refractory atopic dermatitis and poor response to eczema medications (topical steroids, oral antihistamines) were enrolled.

METHODS. This was a prospective, double-blind, placebo-controlled trial in which patients were randomly assigned at a ratio of 2:1 to receive XFS or placebo over 8 weeks. There were 47 (median age: 12.2 years) given XFS and 24 (median age: 13.6 years) given placebo. Participants were matched according to gender, height, weight, BMI, age, duration of illness, and symptom scores. Patients were given varying doses depending on age. Laboratory studies were performed and total lesion score, erythema score, surface damage score, pruritus score, and sleep scores were calculated at 4-week intervals up to 12 weeks.

RESULTS. A total of 56 subjects completed the entire study. There was a statistically significant improvement in total lesion scores among those in the treatment group compared to those of the placebo group ($79.7 \pm 5.8\%$ vs $13.5 \pm 7.64\%$; $P < .001$). There was also statistically significant improvement in all symptom scores for those on treatment compared to those on placebo. Four weeks after the treatment was discontinued, the mean improvement in the clinical lesion score for the XFS group was still significantly better than that of the placebo group. Patients reported no adverse effects except unpalatability for some. Treatment did not affect total serum immunoglobulin E level, eosinophil counts, or interleukin 5, interleukin 13, or eosinophil cationic protein levels.

CONCLUSIONS. The traditional Chinese herbal medication XFS might be an alternative choice of therapy for severe, refractory, extensive, nonexudative atopic dermatitis.

REVIEWER COMMENTS. Severe and widespread atopic dermatitis can be frustrating to treat for patients, parents, and physicians. Patients often ask their physicians if there are alternative approaches to controlling atopic diseases. XFS is a common Chinese herbal preparation of 12 herbs, some with known anti-inflammatory effects, that might provide a complementary option for adults and children who require systemic steroids to control their eczema flares. However, more scientific evaluation of XFS to determine its mechanism of action, safety profile, applicability, and palatability need to be considered before widespread use is accepted.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2011-2107BBBB

Joann H. Lin, MD
McKinney, TX

PRIMARY IMMUNODEFICIENCY, HIV, AND INFECTIOUS DISEASES

Chronic Mucocutaneous Candidiasis in Humans With Inborn Errors of Interleukin-17 Immunity

Puel A, Cypowyj S, Bustamante J, et al. *Science.* 2011; 332(6025):65-68

PURPOSE OF THE STUDY. Chronic mucocutaneous candidiasis disease (CMCD) is characterized by recurrent or persistent infections of the skin, nails, and oral and genital mucosa caused by *Candida albicans* and sometimes *Staphylococcus*. Previous studies have shown that interleukin 17 (IL-17) receptor-deficient mice were more susceptible to oropharyngeal candidiasis and staphylococcal infections of the skin. The purpose of this study was to assess if findings in the mouse model also applied to humans.

METHODS. Candidate gene sequencing was performed on a child with *C albicans* in the neonatal period and *Staphylococcus aureus* dermatitis at 5 months of age and a family from Argentina with autosomal dominant pattern of CMCD inheritance. Sequences of IL-17-related genes and receptors from affected people were compared with those of family members and controls. Additional experiments were performed by incubating fibroblasts from an affected child with recombinant IL-17A and IL-17F homodimers and heterodimers.

RESULTS. The initial child was found to be homozygous for a mutation in the *IL17RA* gene that was not found in any of the controls. The IL-17RA protein was not detected on the surface of fibroblasts, CD4⁺ T cells, CD8⁺ T cells, or monocytes from the patient. The patient's fibroblasts did not respond to any of the 3 IL-17 cytokines. In the family

studied, a heterozygous missense mutation was found in the *IL17F* gene. The mutant allele was found in 2 apparently healthy family members, which suggests incomplete clinical penetrance, and in all of the affected members of the kindred. This mutant protein was tested in a cell line and was nonfunctional.

CONCLUSIONS. Mutations in IL-17–family genes that cause functional deficiency of this pathway are associated with CMCD.

REVIEWER COMMENTS. This is an excellent example of bench-to-bedside medicine and illustrates the utility of murine models of immunity in the search for causes of human disease. These findings provide definitive evidence that IL-17A and IL-17F are essential for protective immunity to *C albicans* and, to a lesser extent, *S aureus* in the nails, skin, and oral and genital mucosa and provide new opportunities for designing novel treatments for this chronic immunologic disorder. It is also important to consider that elevated levels of IL-17 have been associated with various chronic inflammatory conditions, which raises the possibility that anti-IL-17 treatment strategies now under development could lead to increased susceptibility to infections with *C albicans* or *S aureus*.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2011-2107CCCC

Douglas F. McMahon, MD
James E. Gern, MD
Madison, WI

Hypomorphic *Rag* Mutations Can Cause Destructive Midline Granulomatous Disease

De Ravin SS, Cowen EW, Zarembek KA, et al. *Blood*. 2010;116(8):1263–1271

PURPOSE OF THE STUDY. To describe a new clinical phenotype in patients who inherit mutations in the recombination activation gene (*Rag*) necessary for effective immunoglobulin and T-cell receptor gene rearrangement.

STUDY POPULATION. This was a case report of a 14-year-old patient referred with a 1-year history of extensive granulomatous destruction of the midface structures and a past history of myasthenia gravis treated with thymectomy. The patient had a sister who died at 5 years of age of staphylococcal sepsis; she also had a history of ptosis that the authors suggested might have reflected undiagnosed myasthenia gravis.

RESULTS. The patient underwent extensive immunologic and genetic testing for both autoimmune disease and immunodeficiency disorders that revealed compound heterozygous mutations in *Rag*. These mutations resulted in ~50% loss of Rag enzyme functional activity. The immunologic studies revealed relatively normal T

and B cells and normal immunoglobulin levels and T-cell diversity but markedly decreased FoxP3⁺ T-regulatory cells.

CONCLUSIONS. Immune dysregulation with granulomatous hyperinflammation and autoimmunity can result from hypomorphic mutations in the gene encoding Rag.

REVIEWER COMMENTS. This study adds to the phenotypic range of disease that is now associated with mutations in the *Rag* gene, which now include classical severe combined immunodeficiency, Omenn syndrome, combined immunodeficiency with expansion of γ - δ T cells, granulomatous disease, and autoimmunity. Readers are encouraged to refer to a recent review in which phenotypic variability based on cases with RAG1 deficiency was demonstrated (Valayannopoulos V, de Blic J, Mahlaoui N, et al. *Pediatrics*. 2010;126[5]; available at: www.pediatrics.org/cgi/content/full/126/5/e1242). Recognition of variable phenotypes with mutations in a gene associated with primary immunodeficiency disorders has become a common phenomenon, which clearly suggests that practitioners must be aware that “textbook” descriptions of gene defects associated with primary immunodeficiencies only present part of the full story and that the potential for phenotypic variability is significant.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2011-2107DDDD

Thomas A. Fleisher, MD
Bethesda, MD

Clinical Disease Caused by *Klebsiella* in 2 Unrelated Patients With Interleukin 12 Receptor β 1 Deficiency

Pedraza S, Lezana JL, Samarina A, et al. *Pediatrics*. 2010;126(4). Available at: www.pediatrics.org/cgi/content/full/126/4/e971

PURPOSE OF THE STUDY. To describe a new infectious disease phenotype in patients who inherit mutations in the interleukin 12 (IL-12) signaling pathway.

STUDY POPULATION. In this report the authors documented sepsis with *Klebsiella pneumoniae* in 2 unrelated patients with complete defects in the IL-12 receptor β 1.

METHODS. This was a chart review with case reports.

RESULTS. The first patient was born to unrelated parents and developed BCGitis after BCG vaccination in infancy followed by nontyphoidal salmonellosis. Both infections were difficult to treat despite multiple appropriate antimicrobial agents administered over 26 months. This was followed by development of disseminated *Mycobacterium bovis* infection, which also responded poorly to multi-drug antimicrobial agents along with interferon γ therapy. The patient’s condition worsened, and he developed

Chronic Mucocutaneous Candidiasis in Humans With Inborn Errors of Interleukin-17 Immunity

Douglas F. McMahon and James E. Gern

Pediatrics 2011;128;S140

DOI: 10.1542/peds.2011-2107CCCC

Updated Information & Services

including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/128/Supplement_3/S140.2

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Allergy/Immunology
http://www.aappublications.org/cgi/collection/allergy:immunology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Chronic Mucocutaneous Candidiasis in Humans With Inborn Errors of Interleukin-17 Immunity

Douglas F. McMahon and James E. Gern

Pediatrics 2011;128;S140

DOI: 10.1542/peds.2011-2107CCCC

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/128/Supplement_3/S140.2

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2011 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

