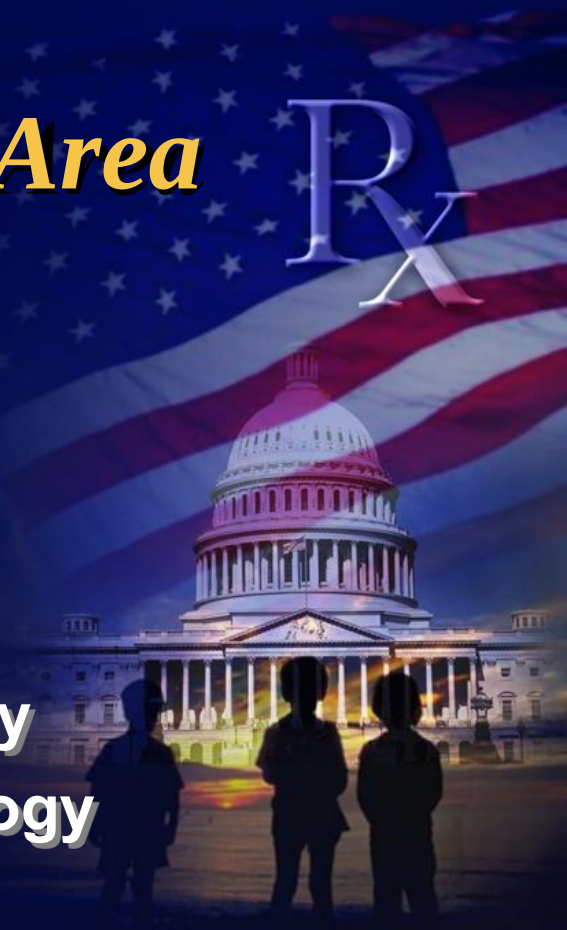
Dermatology Therapeutics Area Working Group



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Overview

- Background
- Identified Areas of Therapeutic Need with Committee Recommendations

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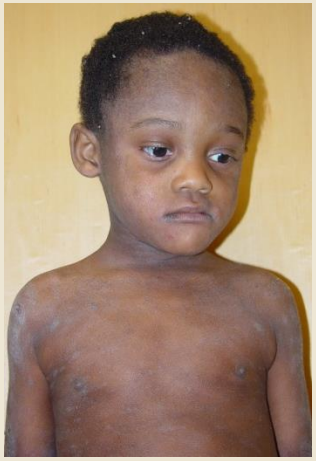
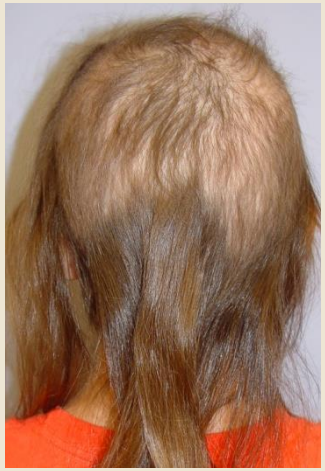
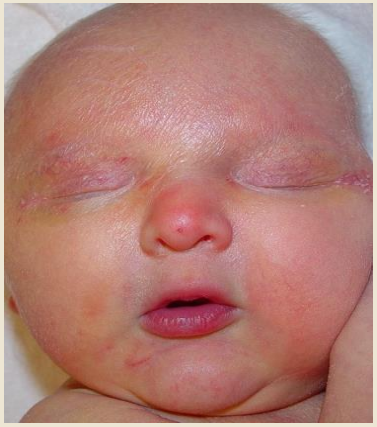
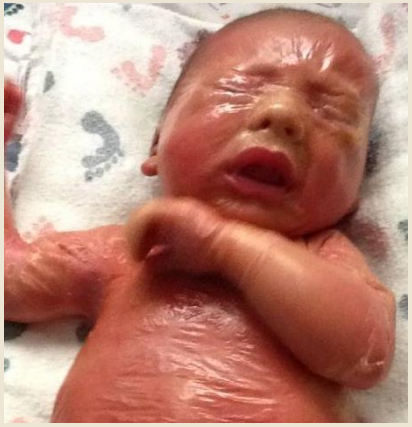
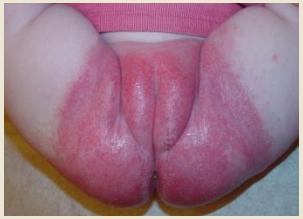
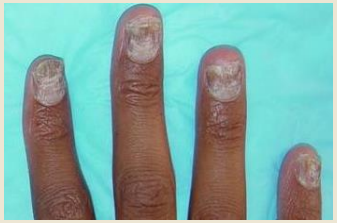
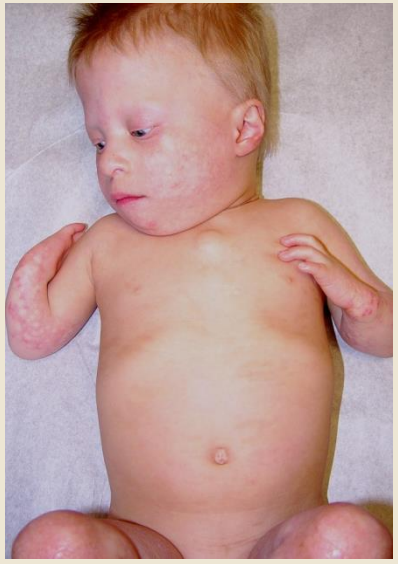
Pediatric Dermatology Background

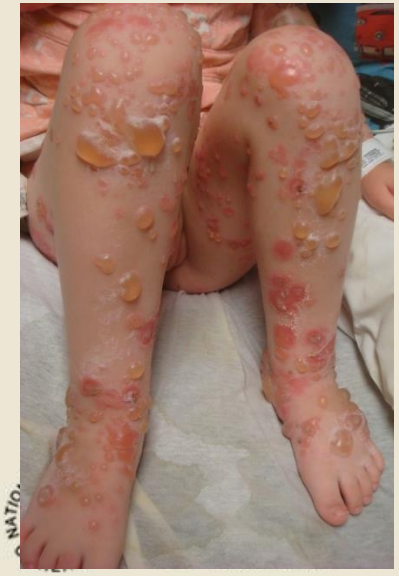
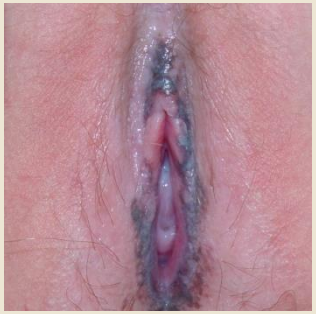
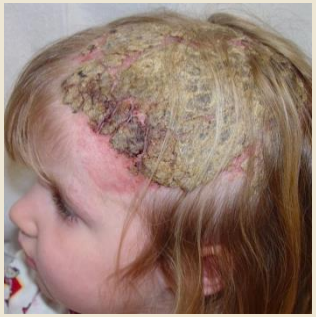
- *High Demand*
- **Small Workforce**
- **Ambulatory-Based**
- **Medical>Procedural**
- **Limited Evidence-Basis**
- ***Few FDA-Approved Treatments***

Skin-Related Disease in Children

- Up to 30% of pediatric primary care visits
- ER/hospital consultation>direct hospital admissions
- Limited OR utilization
- The majority without FDA-approved treatment

Workforce

- Society for Pediatric Dermatology (www.pedsderm.net)
  - 1,000 members
  - 45 states
  - 37 countries

ABD Subspecialty Certification		
Year	**# (%) Completing a Fellowship**	**# (%) Passing the Exam**
2004	24 (25)	90 (96)
2006	3 (10)	41 (93)
2008	18 (58)	31 (91)
2010*	24 (63)	33 (91)
2012	43 candidates (95)	NA
Total	**~200 (80)**	**~235 (94%)****

***Last year for grandfather eligibility**

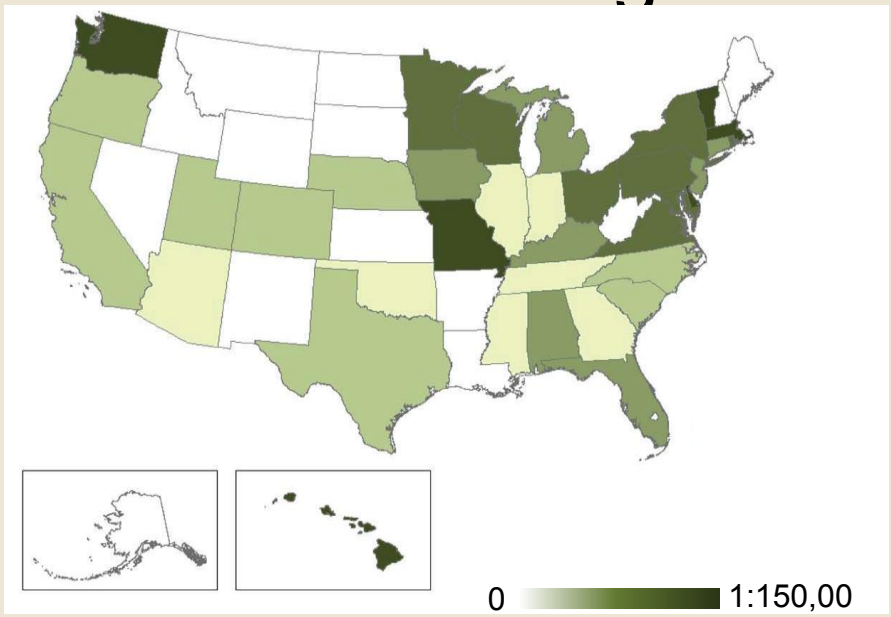
****~60% qualified by meeting grandfather criteria.**

Workforce Shortage: Comparative Supply

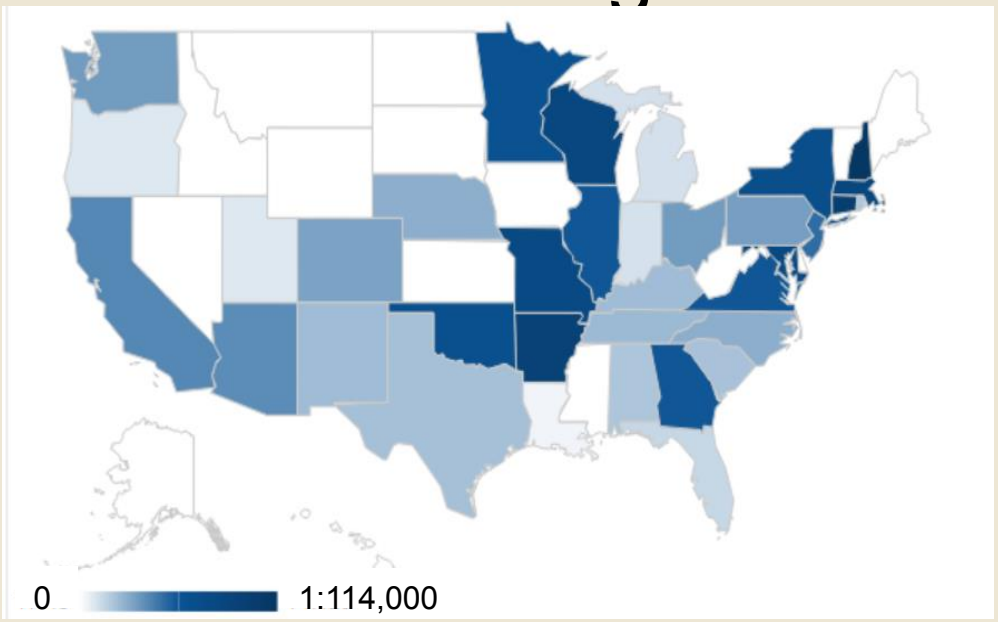
US Specialty	Per Capita Supply
Dermatologists	30,000 people
Pediatricians	1,500 people <18
Pediatric Rheumatologists	240,000 people <18
Pediatric Dermatologists	385,000 people <18

Workforce Shortage: Comparative Density

Rheumatologists



Dermatologists



Pediatric Subspecialist-to-Child Ratio

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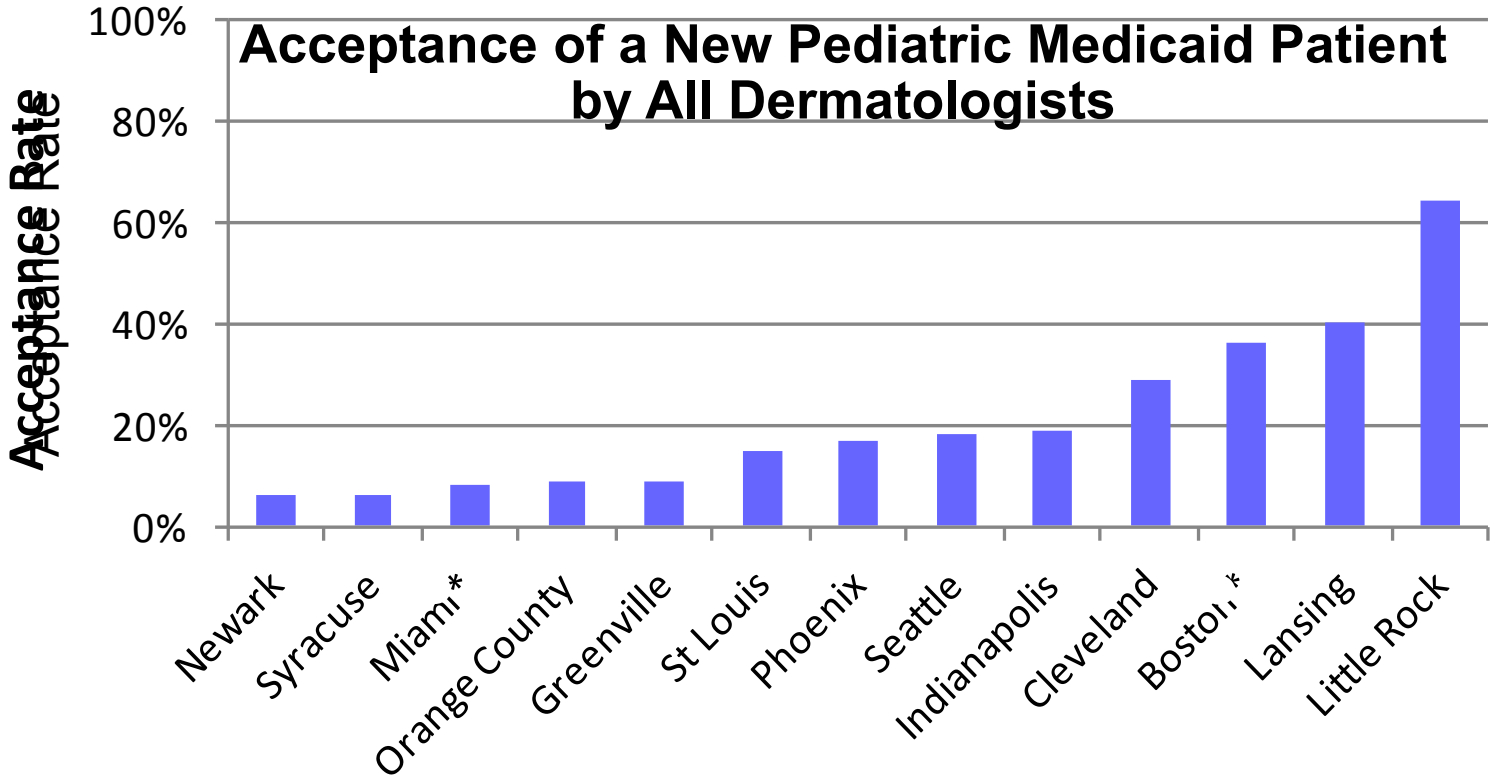
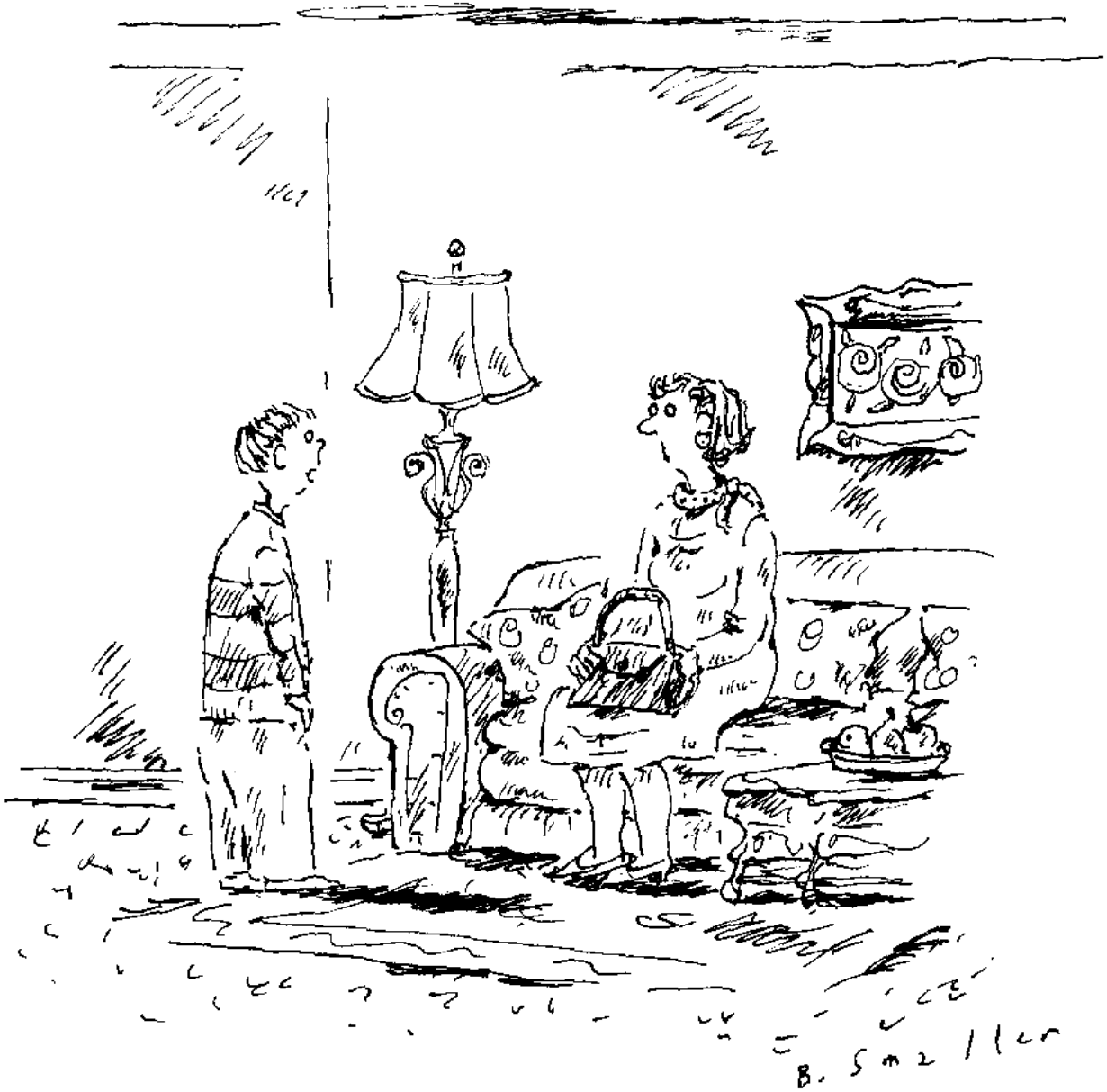
Workforce Shortage:



Average overall market size-weighted acceptance rate: 19%

Chaudhry S , Siegfried EC, Armbrecht E. Pediatric access to dermatologists: Medicaid vs. private insurance. J Am Acad Dermatol. In press..



"When I grow up, I want to go into medicine and help people who can pay out of pocket."

Thank You

- **BPCA**
- **NICHD**
- **FDA**

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Dermatology Therapeutic Area Working Group Members

- *Rosemary Addy, M.H.S.*
- *Carl C. Baker, M.D., Ph.D.*
- *Kimberley W. Benner, Pharm.D.*
- *Katherine Berezny, M.P.H.*
- *Julie Block*, CEO, National Eczema Association
- *Jeffrey Blumer, M.D., Ph.D.*
- *Denise Cook, M.D.*
- *Beth Drolet, M.D.*
- *Linda Duffy, Ph.D., M.P.H.*
- *Beth Durmowicz, M.D*
- *Lawrence Eichenfield, M.D.*
- *Roselyn Epps, M.D.*
- *Jacqueline Francis, M.D., M.P.H.*
- *Norma Gavin, Ph.D.*
- *Adelaide Hebert, M.D.*
- *Maria K. Hordinsky, M.D.*
- *Thomas Hultsch, M.D., Ph.D.*
- *Wendla Kutz, M.S.N, C.N.S.*
- *Marie Ann Leyko, Ph.D.*
- *Anne Lucky, M.D.*
- *Martha Nguyen, J.D.*
- *Ian M. Paul, M.D., M.Sc.*
- *Hanna Phan, Pharm.D.*
- *Denise J. Pica-Branco, Ph.D.*
- *Merrily Poth, M.D.*
- *Hari Cheryl Sachs, M.D.*
- *Alex Silver*
- *Gina Simone*
- *Donna Snyder*
- *Perdita Taylor-Zapata, M.D.*
- *Katerina Tsilou, M.D.*
- *Surendra K. Varma, M.D*
- *Kelly Wade, M.D., Ph.D.*
- *Jonathan K. Wilkin, M.D.*
- *Teri Woo, Ph.D., R.N.*
- *Lynne P. Yao, M.D.*
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Identified Areas of Therapeutic Need

- Atopic Dermatitis
- Hemangioma of Infancy
- Epidermolysis Bullosa & Other Genodermatoses
- Pediatric Dermatology Drug Development

Atopic Dermatitis

Subcommittee Members

- Larry Eichenfield, M.D.
- Adelaide Hebert, M.D.
- Julie Block
- Hanna Phan, Pharm.D.
- Kimberly Benner, Pharm.D.

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Atopic Dermatitis-Clinical Features

- Chronic, recurrent, inflammatory skin disease characterized by widespread redness, edema, scaling, crusting
- Severe itch often interrupting sleep for multiple family members.
- Lifelong tendency towards dry skin, occupational skin disease, skin infections, eye problems, disrupted family and social relationships, and work/school absenteeism

Atopic Dermatitis-Pathogenesis

AD is a phenotype, representing a group of conditions caused by genetic and environmental factors responsible for

- Skin barrier defects
- Increased susceptibility to bacterial, viral, fungal skin infections
- Immune dysfunction

Atopic Dermatitis-Epidemiology

- **Onset < 2 years in 80%**
- **8-15% childhood prevalence**
  - 60% - mild, spontaneous improvement over ~10 yr
  - 35% - persistent with a range of associated problems
  - 5% - severe lifelong disease
- **300% rise in prevalence over the past 30 yr**
- **Strong genetic link with other allergic conditions**
  - food allergy(15-30%)
  - asthma (50%)
  - allergic rhinoconjunctivitis (66%)
  - eosinophilic esophagitis/gastroenteritis

Atopic Dermatitis- Non-Allergic Comorbidities

- **Sleep deprivation**
- **Neuropsychiatric**
  - ADHD
  - anxiety, depression
  - autism
- **Poor growth***
- **Osteopenia***
- **Cataracts***

* Possibly corticosteroid-related

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Atopic Dermatitis-Therapeutic Issues

- **Early therapeutic intervention and disease control may favorably impact progression and comorbidities.**
- **Poor adherence is a common cause of treatment failure.**
- **Obstacles to adherence**
  - No well-defined standard-of-care
  - Conflicting recommendations
  - Medication phobia
  - Labeling/access restrictions
  - Topical treatment is time-consuming, complex and difficult to master.

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Atopic Dermatitis- Principles of First-Line Treatment

- **Skin care education**
  - Avoid complex topical products
  - Bathing
  - Emollient
- **Control itch and skin infection**
- **Topical Rx**
  - Corticosteroids
  - Calcineurin inhibitors

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Pediatric Indication FDA-Approved Topical Corticosteroids

Product	Age group	Frequency of Application	Duration of Tx
clobetasol propionate 0.05% foam	> 12 yr	2 times daily	2 wk
fluocinolone acetonide 0.01% scalp oil	> 12 yr	2 times daily	2 wk
mometasone 0.1% cream/ointment	> 2 yr	1 time daily	3 wk
fluticasone 0.05% lotion	> 1 yr	1-2 times daily	4 wk
aclometasone 0.05% cream/ointment	> 1 yr	2-3 times daily	2 wk
prednicarbate 0.1% cream/ointment	> 1 yr	1-2 times daily	3 wk
fluticasone 0.05% cream	> 1 yr	1-2 times daily	4 wk
desonide 0.05% foam/gel	> 3 mo	2-3 times daily	4 wk
hydrocortisone butyrate 0.1% cream	> 3 mo	2-4 times daily	4 wk
fluocinolone acetonide 0.01% body oil	> 3 mo	3-4 times daily	2 wk

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FDA-Approved Topical Calcineurin Inhibitors (TCI)

Product	Age group	Frequency of Application	Duration of Tx
pimecrolimus cream 1%	≥ 2 yr	2 times daily	>1 yr
tacrolimus ointment 0.03%	≥ 2 yr	2 times daily	>1 yr
tacrolimus ointment 0.1%	≥ 18 yr	2 times daily	>1 yr

Indication: ”second-line therapy for the short-term and non-continuous chronic treatment of AD in non-immunocompromised adults and children [≥2 years of age] who have failed to respond adequately to other topical prescription treatments for [AD], or when those treatments are not advisable”

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Pimecrolimus Cream Enrollment Clinical Trials Reviewed at Approval Nov. 2001

Phase 3 Controlled Studies/Pivotal	Duration of Exposure	# Exposed subjects
Pediatric (2-17 years)	26 wk	130
Pediatric (2-17 years)	26 wk	137
Infants (<2 years)	26 wk	123
Controlled Supportive Safety		
Infants (<2 years)	6 mo[b]	204
Pediatric (2-17 years)	1 yr	474
Adults (≥18 years)	1 yr	328
TOTAL		1,396
Infants (<2 years)	6 mo – 1 yr	327
Children (2-17 years)	**6 mo – 1 yr**	**741**
Adults (≥18 years)	**1 yr**	**328**

US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Elidel NDA 21-302 medical review, November 6, 2001. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-302_Elidel.cfm. Accessed January 23, 2012.

TCI Labelling Change

- Q4 2003 TCI Rx: 11% to infants <2 yr
- Oct. 2003 FDA PAC for product registry protocol review; AERS malignancy reports shifted focus of the meeting
- Jan. 2006 boxed warning based on a theoretical risk of malignancy

Siegfried EC, Jaworski JC, Hebert AA. Low risk associated with use of topical calcineurin inhibitors: review of the evidence and implications for daily practice. Submitted for publication.

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Outcomes

- **Abrupt decrease in Rx (esp. infants)**
  - Caregiver phobia
  - Provider hesitation
  - Third-party payor restriction
- **Epidemiological/clinical studies without TCI/lymphoma link**
- **Mandated post-marketing surveillance studies in process**

Siegfried EC, Jaworski JC, Hebert AA. Low risk associated with use of topical calcineurin inhibitors: review of the evidence and implications for daily practice. Submitted for publication.

Pimecrolimus Cream Enrollment- All Clinical Trials as of May 2010

Age	Duration of Exposure	# Subjects Exposed
Infants (<2 years)	≤6 yr	~10,000
Children (2-17 years)	≤10 yr[c]	~21,000
Adults (≥18 years)	≤3 yr	~16,000
Other Age Ranges:		
≥3 months	≤26 wk	~350
3 months-17 years	≤27 wk	~100
1-4 years	≤12 wk	~75
≥2 years	≤18 wk	~5,600
>10 years	≤12 wk	~2,200
Unspecified	≤3 yr	~450
TOTAL		**>55,000**

Committee Recommendations

- **Reevaluate the evidence**
- **Revise labeling to reflect safety and efficacy of pimecrolimus cream in infants ≥ 3 months**
- **Remove the boxed warning if the evidence is lacking.**

Severe Atopic Dermatitis- Beyond Topical Therapy

- No FDA-approved systemic therapy
- Off-label, level 3 evidence-based Rx: immunosuppressive and cytostatic agents (cyclosporine, azathioprine, mycophenolate mofetil, methotrexate); immunomodulators (IVIG, IFN-gamma)
- Few adult-only trials of new chemical entities (anti-IL-4, oral phosphodiesterase inhibitors)

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Severe Atopic Dermatitis- Existing Resources

- International core outcomes consortium: Harmonizing Outcome Measures for Eczema (HOME)
- US multicenter research network: Pediatric Dermatology Research Alliance (PeDRA)-Inflammatory Skin Diseases Group unfunded comparative study of cyclosporine, azathioprine, mycophenolate mofetil and MTX (NCT01447381)

Committee Recommendations

- Provide funding to expand clinical trials of systemic therapies for severe AD initiated by PeDRA.
- Encourage drug comparison efficacy studies, rather than placebo-controlled trials.
- Include children as young as age 2 with severe AD in trials involving systemic immunosuppressant medications and new chemical entities.
- Develop and validate standardized outcomes measures for pediatric AD across the age spectrum.

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Genodermatoses

Subcommittee Members

- Anne Lucky, M.D.
- Adelaide Hebert, M.D.
- Elena Pope, M.D.
- Megha Tollefson, M.D.
- Wynnis Tom, M.D.

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Genodermatoses

Epidermolysis bullosa (EB) is a rare, inherited condition of skin fragility and blistering, significant early morbidity and mortality.

- Herlitz-Junctional EB (JEB-H): usually fatal in the first months or years of life
- Recessive Dystrophic EB (RDEB): crippling skin and systemic morbidities; shortened life span.
- EB simplex (EB Dowling-Meara): increased neonatal morbidity and mortality

Genodermatoses

- **Comorbidities**
  - Poor wound healing
  - Impaired nutrition and failure to thrive
  - Secondary infection
  - Chronic itch and pain
  - Anemia
  - Osteoporosis, pathologic fractures
  - Loss of hand function
  - Isolation from peers and society
- **The costs of managing EB are high**
- **Optimal care is via tertiary centers that support a coordinated team.**
- **No FDA-approved therapeutic agents are available for any subtype or age group.**

Genodermatoses

- **15 genes have been identified to cause various forms of EB.**
- **Recent therapeutic strides applicable to patients with severe forms of EB:**
  - Methodology for gene replacement
  - Protein replacement
  - Biologic therapy

Committee Recommendations

- **Provide funding to expand the EB Clinical Research Consortium national registry/database**
  - Centralize genetic testing results
  - Identifiy potential subjects for clinical trials
- **Registry expansion should occur in parallel with clinical studies to allow maximum progress.**

Committee Recommendations

- Support studies to test and validate outcome measures.
- Initiate therapeutic trials in adults.
- Define inclusion criteria for children with severe EB subtypes to enable early enrollment in the same trials.
- Develop parameters to maximize safety for the youngest age groups.
- Encourage fast-track FDA approval for EB drugs.

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Hemangioma of Infancy

Subcommittee Members

- **Beth Drolet, M.D.**
- **Kelly Wade, M.D.**
- **Elena Pope, M.D.**
- **Megha Tollefson, M.D.**

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Hemangioma of Infancy

- The most common tumor of childhood
- ~ 80,000 infants/yr in the US
- Complications necessitating treatment (~12%): disfigurement, ulceration/pain, visual impairment, airway obstruction, congestive heart failure
- No FDA-approved treatments; 1 industry-sponsored, phase II/III international multicenter, PCDB trial
- Existing research network (HIG; Hemangioma Investigator Group)

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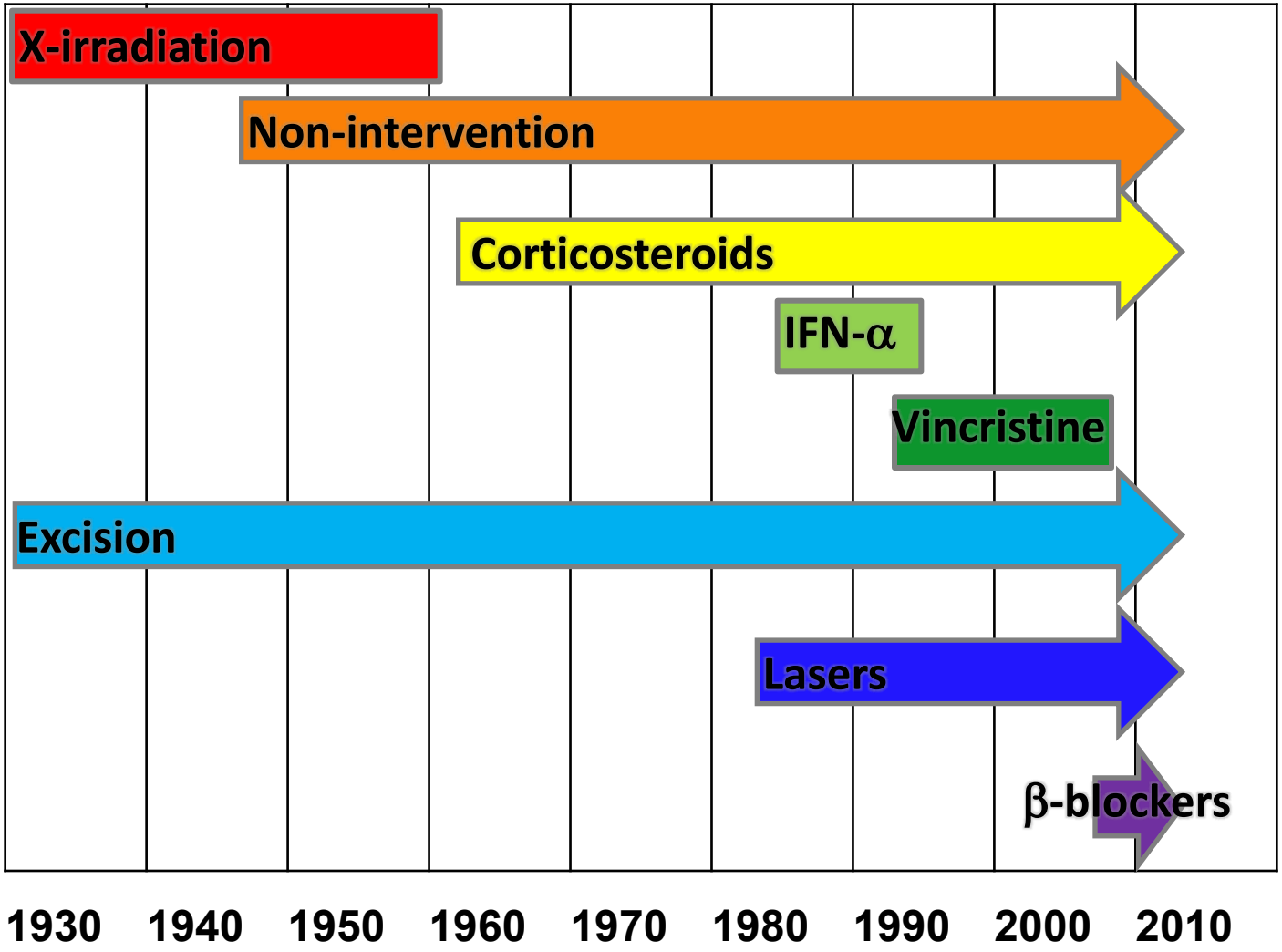
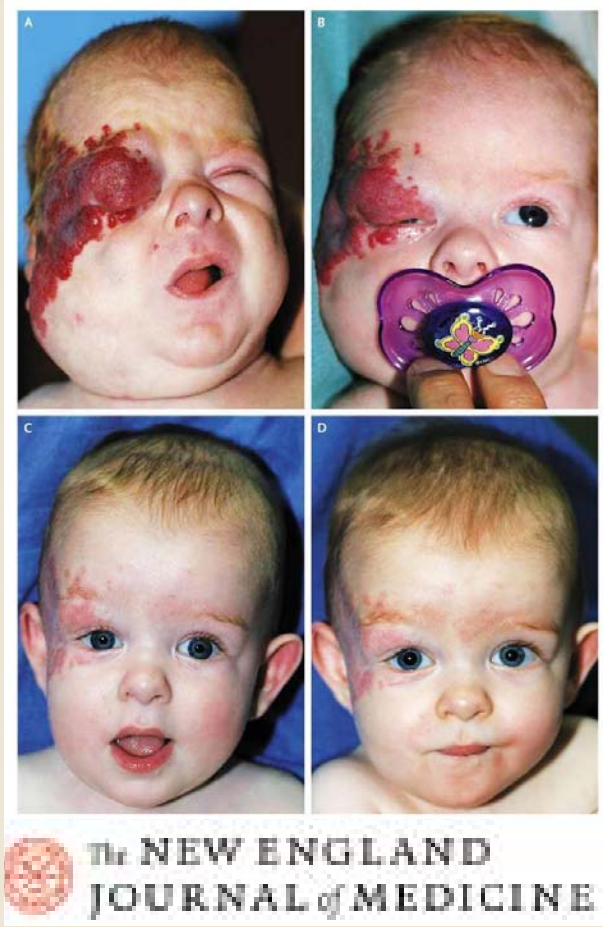
Hemangioma of Infancy: Treatment Options



Itinteang T, Withers AH, Leadbitter P, Day DJ, Tan ST. Pharmacologic therapies for infantile hemangioma: is there a rational basis? Plast Reconstr Surg. 2011;128(2):499.

β-blocker Treatment for Hemangioma of Infancy



- Index case failed high dose IV corticosteroids
- Treatment complicated by hypertrophic cardiomyopathy
- Incidental rapid improvement
- Open-label treatment of 10 additional cases
- Published as a short communication (400 words)
- 268 publications as of 11/25/12

Léauté-Labrèze C et al. Propranolol for evere hemangiomas of infancy. 2008 Jun 12;358(24):2649-51.

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β-blocker Treatment for Hemangioma of Infancy

- **Off-label oral and topical beta blockers have rapidly been adopted as first line therapy.**
- **Propranolol suspension**
  - 30,000 more Rx 2011 vs. 2007, *including complicated HOI*
  - Pierre-Fabre sponsored phase II/III multicenter, PCDB trial: propranolol in an optimized suspension; (planned FDA submission 1/07/13); *this protocol excludes complicated HOI.*
- **Propranolol gel: Pierre Fabre (proof of concept)**
- **Timolol ophthalmic (0.5% or 0.1% GFS)**
  - 4-10X more potent than propranolol
  - AEs (4% of children on intraocular timolol for glaucoma): bradycardia, hypoglycemia, and wheezing
  - Anticipated Rx for 10% HOI = 80 fold increase compared to infantile glaucoma

Oral β-blocker Clinical Needs

- **Additional safety/efficacy information**
- **Propranolol (generic suspension, nadolol? atenolol?)**
- **Validation for consensus-derived guidelines***
  - Monitoring
  - Dose escalation
  - Initiation < 2 mo
  - Use in pre-term infants
  - Use in PHACE/LUMBAR syndrome
  - Duration of treatment
  - Discontinuation

*Drolet B et al. Pediatrics, in press

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Topical β-blocker Clinical Needs

- **Propranolol gel, ophthalmic preparations: timolol,?betaxolol)**
- **Safety/efficacy/PK**
- **Oral/topical comparative data**
- **Dosing**
- **Indications**
  - Ulceration
  - Periorbital lesions
  - Premature infants, especially <2 mo old

Committee Recommendations

- **If Pierre Fabre oral propanolol receives FDA approval for *uncomplicated* HOI, there remains a desperate need for additional studies to evaluate safety/efficacy of oral propranolol for *complicated cases*.**
- **Utilize expertise within PTN, NICHD, HIG and industry to design & perform**
  - Standardized safety reporting protocol to track likely AEs for infants enrolled in β-blocker studies
  - Phase I/II studies of percutaneous application of timolol maleate ophthalmic solution

Pediatric Dermatology Drug Development Issues

Subcommittee Members

- Elaine Siegfried, M.D.
- Jon Wilkin, M.D.
- Larry Eichenfield, M.D.
- Roselyn Epps, M.D.
- Maria Hordinsky, M.D.
- Surendra Varma, M.D.
- Teri Moser Woo, R.N., Ph.D.

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Pediatric Dermatology Drug Development Issues- Introduction

Many skin-related conditions are

- common
- costly in economic terms
- chronic
- cause significant morbidity
- carry substantial comorbidity risks
- generate emotional distress
- markedly impair quality of life for the affected child and family

Pediatric Dermatology Drug Development Issues- Introduction

"Quality-of-life illnesses are disorders that are regarded as unimportant to those who don't have them."

-Ray Slavin, M.D.

"Skin disease won't kill you, but it can ruin your life."

-Elaine Siegfried, M.D.

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Pediatric Dermatology Drug Development Issues- Introduction

The unmet need is high for safe/effective treatments for children with chronic and severe pediatric dermatologic diseases.

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Pediatric Dermatology Drug Development Issues- Introduction

Major obstacles hinder new drug development for pediatric skin diseases

- Product labeling that overemphasizes *theoretical* risks of new treatments compared to *well-established* risks of poorly controlled, chronic disease
- Underappreciated risks of AEs from widespread off-label use of drugs that lack evidence-based treatments
- No well-defined risk parameters or guidelines for development of new drugs in children with non-lethal, but life-altering disorders

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Pediatric Dermatology Drug Development Issues- Goals

- To state the need for well-defined regulatory clinical development pathways to inform, facilitate and incentivize new treatments for severe and chronic pediatric skin diseases.
- To generate an official request to seek input from experts in order to draft a guidance document for FDA review and modification per the Current Good Guidance Document Practices.
- To offer initial suggestions for inclusion into a Level 1 Guidance Document for New Drug Development in Pediatric Dermatology

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Pediatric Dermatology Drug Development Issues- Guidance Document Suggestions

- Develop optimal packaging to assist in delivery of appropriate amounts of topical medication
- Determine optimal topical dosing quantities
- Do not postpone early phase drug trials in infants and children until after efficacy is determined in adults.
- Do not exclude drugs that have not achieved proven efficacy in adults as presumably ineffective in children.
- Do not place higher priority on theoretical risks of new drugs than established morbidity and impact on QOL for pediatric skin disease.

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Pediatric Dermatology Drug Development Issues- Guidance Document Suggestions

- Determine age limits for initial trials based on the drug and the disease, e.g.
  - Include premature infants with a newly detected HOI in trials for of a topical beta-blocker.
  - Include children as young as age 2 with severe AD in trials involving systemic immunosuppressant medications.
- Apply adverse event data for drugs that have been studied for other pediatric indications to further study of skin disease in children.

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Pediatric Dermatology Drug Development Issues- Guidance Document Suggestions

- Be aware of the Harmonizing Outcome Measures for Eczema (HOME) project (http://www.homeforeczema.org): experts working together to agree on core set of outcome measures for use in all AD clinical trials.
- HOME III will be held 4/6/13 in San Diego, CA. Representatives from the EMEA will be participating. Similar FDA participation would be optimal.

Pediatric Dermatology Drug Development Issues- Guidance Document Suggestions

- Incorporate input from parents of affected children in clinical trials protocol design via surveys seeking parental opinion on
  - tolerable washout periods
  - acceptable duration for placebo exposure
  - achievable frequency of study visits
  - tolerable number of phlebotomies and skin biopsies
  - worthwhile outcomes
- Require use of microtainer technology for routine hematology and chemistry assays.

Pediatric Dermatology Drug Development Issues- Guidance Document Suggestions

Support the Pediatric Dermatology Research Alliance (PeDRA), a currently unfunded network to facilitate design and conduct of clinical trials, share resources and garner sufficient cohorts to study pediatric skin diseases.

- Hemangioma Investigator Group (HIG)
- Epidermolysis Bullosa Clinical Research Consortium (EBCRC)
- Pediatric Inflammatory Skin Diseases Group (PISDG)

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Pediatric Dermatology Drug Development Issues- Committee Recommendations

- **Recognize new drug development as a significant unmet need for children with severe and chronic skin disease.**
- **Appreciate the importance of an FDA-issued guidance document relevant to new drug development for children with severe and chronic, but non-life threatening skin diseases.**

Pediatric Dermatology Drug Development Issues- Committee Recommendations

- **The committee is aware that 21CFR10.115 specifically encourages submission of subjects and drafts to the FDA for consideration and modification towards creating guidance documents.**
- **Apply background information provided towards developing a level 1 guidance document for new drug development for the top 3 identified areas of need: hemangioma of infancy, epidermolysis bullosa and atopic dermatitis as a first priority.**

Pediatric Dermatology Drug Development Issues- Committee Recommendations

- **Provide additional support to convene a working group of experts to create an initial draft for review and modification by FDA.**
- **The ideal working group would include participants with expertise in**
  - Clinical care of children with skin disease
  - Drug development for skin disease
  - Pediatric drug development
  - Guidance document design