A DERMATOLOGY FOUNDATION PUBLICATION

SPONSORED BY ORTHO DERMATOLOGICS

VOL. 38 NO. 2 FALL 2019

DERMATOLOGY FOCUS™

DF Clinical Symposia: Proceedings 2019–Part II

ADVANCES IN DERMATOLOGY

The Dermatology Foundation presented its annual 3-day cutting-edge CME symposia series earlier this year. Informal Breakfast Roundtables and evening Therapeutics Forums amplified the take-home value. Part II of the Proceedings includes Therapeutic Updates; Diagnostic Dilemmas; and Medical Dermatology. (Part I, which appeared in the previous issue, included the Keynote talk on Treating to Target in Psoriasis; Challenges in the Dermatology Clinic; Special Populations; CPC Session; and Cutaneous Oncology).

MINI-SYMPOSIUM: THERAPEUTIC UPDATES

Practical Management of Challenging Atopic Dermatitis in 2019

Sheilagh M. Maguiness, MD

Introduction. Dr. Maguiness described the typical first visit of a new family. They have been caring for their child with severe AD, which has an impact on quality of life estimated as equal to that of living with Type I diabetes. Families arrive with extensive myth, misinformation, and a sense of fatalism because they are convinced they tried everything and it has all failed them. Then Maguiness detailed the intensive educational and therapeutic elements that typically take the patient from severe to clear—with only a few residual hotspots—in just 2 weeks. She also discussed the "practice-changing" preventive measures instituted at birth for at-risk infants—regular bathing followed by a bland emollient—and introduced the emerging pediatric use of the biologic dupilumab, "the cusp of a new era in eczema management."

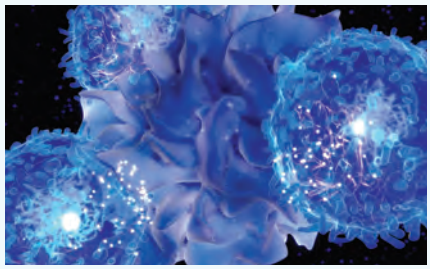
The therapeutic elements. Essential is "investing the time at the first visit to educate the parents and build that therapeutic alliance." Explaining that the child's skin barrier has a structural defect enables parents to understand the involvement of inadequate hydration, more bacteria, and increased penetration of antigens and allergens. Then Maguiness explains the need to simultaneously treat the dehydrated skin, itch, inflammation, and infection, and teaches parents the entire 2-week topical "eczema boot camp" routine: bleach baths, topical steroids, emollients, and wet wraps, typically done at home. She reassuringly likens a bleach bath to a swimming pool. Maguiness described the procedures and benefits of bleach baths and wet wraps in detail, provided practical tips for gaining parental confidence and understanding, noted variations to the overall "boot camp" routine, and discussed tapering. Then she shared her excitement about "entering

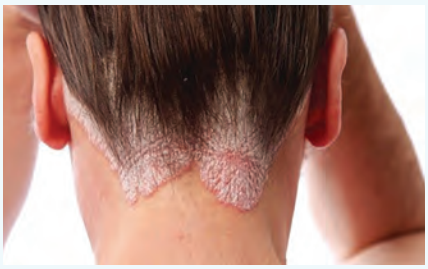
Dupilumab in Children?

- Pediatric asthma indication in October 2018 for ages 12+
  - New 200mg dosing in 1.4 ML syringe
- Clinical trials now underway in children
  - R668-AD-1539 pediatric trial for children 6 months to 6 years (phase II/III)
  - Moderate to severe atopic patients, ages 6 months to 6 years (phase II)
  - Will be particularly useful for mid-childhood AD (ages 5–12)
- **Limitations**
  - Currently ***off-label use*** in patients <12
  - Lack of long-term data: concern for unanticipated long-term complications
  - Access: can be challenging; usually requires peer to peer for insurance authorization
  - We are gaining experience in treating children and adolescents
    - Recent approvals as young as 2 yrs for most-recalcitrant patients
- **Suggested maintenance dosing (following loading):**
  - >60kg: 300mg Q2W (every 2 wks)
  - 20–60kg: 150–200mg Q2W
  - <20kg: ~3–6mg/kg Q2W

(Continued on page 3)

The DF: Where Innovation Begins





The long-term results of the Dermatology Foundation's work are profound. For over 50 years, the DF has focused on furthering patient care by funding innovative research pursued by promising investigators. It has identified and launched a pool of innovators who have brought the specialty a greater understanding of dermatologic diseases—and new treatments—benefiting patients everywhere.

A Case Study: The Advancement of Psoriasis Biology and Therapy

The clinical observation in the 1980s that psoriasis responded to the immunosuppression of cyclosporine generated a groundbreaking paradigm shift in our understanding of the pathogenesis of this disease. Psoriasis as a T-cell mediated immunologic disease became the model from which new clinical and therapeutic discoveries evolved. **The continued progress introduced by DF-funded investigators was tremendous.**

Kevin Cooper, MD, received DF funding in 1986 that contributed to the discovery and development of alefacept, an LFA-3 inhibitor of T cells. In 2003 it became the first biologic therapy approved for psoriasis.

Alice Gottlieb, MD, PhD, studied lymphokine gene expression and sensitivity to cyclosporine in psoriasis with her 1989 DF funding. She became a leading investigative dermatologist, developing and testing novel immunotherapies in clinical trials that correlated clinical responses with immunologic endpoints. This investigative approach accelerated a new pipeline of biologic therapies for psoriasis, and additional DF-funded investigators contributed to its development.

In 2003, **Joel Gelfand, MD, MSCE,** received DF funding to study the incidence of cancer in psoriasis. His work was the first to describe the association of psoriasis with other comorbidities, and it created a new paradigm of psoriasis as a systemic disease. This model was further corroborated when **April W. Armstrong, MD, MPH,** received DF funding in 2009 and demonstrated the association of coronary artery disease with psoriasis.

Wilson J. Liao, MD, received DF funding in 2007 and studied gene expression profiling of clinical responses to etanercept, the first TNF-α inhibitor biologic therapy approved for psoriasis.

Johann E. Gudjonsson, MD, PhD, received DF funding in 2008 to study the biological effects of genetic variation in IL-12B and IL-23R genes in psoriasis. This contributed to approval of the first anti-IL-23 biologic therapy, ustekinumab, for psoriasis in 2009.

Additionally, the 2008 DF funding of **Allen T. Bruce, MD, PhD,** provided support for his study of the phenotype and function of IL-17-secreting T cells in psoriasis. IL-17 targeting led to approvals of the third generation of biologic therapies for psoriasis, which has included secukinumab (2015), ixekizumab (2016), and brodalumab (2017).

Psoriasis patients have benefitted dramatically from the DF's careful investment in the specialty. The DF remains grateful to its dermatologist members, corporate supporters, and society partners who have made the DF's success possible.

Your Support Will Enable Progress

While decades of therapy advances are apparent in every aspect of dermatology, significant challenges remain—conditions still waiting for solutions. **This year, join your colleagues and push the boundaries of change.** Visit dermatologyfoundation.org and become a DF member. ***Your patients will thank you.***

the era of dupilumab—the first systemic for targeted AD use." It has been "life-changing" for the ~40 children she currently treats with it, and the safety profile is very reassuring. Maguiness provided pediatric dosing guidance.

Final comments. "Most patients are colonized or overtly infected, which is why I feel strongly about bleach baths." Intensive topical therapies are safe and effective, even for first-line management. But prevention is still optimal, so identify infants at risk—family history of atopy, or very early signs of skin barrier dysfunction—and begin baths plus emollients.

- **Take-home Pearls**
  - Atopic dermatitis is a disorder of the skin barrier
  - Regular application of emollients in early infancy may reduce the risk of developing AD
  - Almost all patients are colonized/infected—consider regular use of dilute bleach baths
  - Intensive topical therapies are safe and effective in moderate to severe patients
  - We are on the cusp of a new era in eczema management: ***effective biologic therapies***
- **Optimize your success in AD management**
  - **Spend time educating families:** *teach them* the basics
  - As an initial strategy, consider intensive topical therapy with wet wraps
  - Close follow-up is crucial

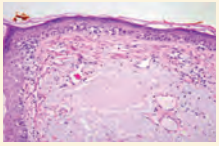
Melanoma of the Head and Neck

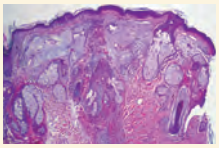
Kishwer S. Nehal, MD

Lentigo maligna (LM) background. This melanoma subtype—which occurs in severely sun-damaged skin with a prolonged history of sun exposure and prior BCC and SCC—represents approximately 15% of melanomas overall and 25% of those in the head and neck region. Mean patient age is 65, with many in their 80s and 90s, but Dr. Nehal is seeing an increasing number of patients in their 40s through 60s. She highlighted the multiple challenges surrounding this melanoma subtype in the head/neck region, including those in the younger patient cohort.

Melanoma—Lentigo Maligna Type: Surgical Management

- Surgery remains standard of treatment
  - Treats periadnexal melano-ctyes
  - Detects unsuspected invasive melanoma
  - Permits histologic assessment of margins
- Head/neck LMM
  - Unpredictable subclinical extension
  - Anatomic and aesthetic considerations





Challenges. *Terminology:* When melanoma *in situ* is referred to as LM, it is commonly misperceived as premalignant and not melanoma. "Yet LM is a melanoma subtype, just as are superficial spreading or acral lentiginous melanoma." LM *is* melanoma *in situ*, and the invasive form is lentigo maligna melanoma (LMM). ***Evaluation:*** Although the typical LM evolves very slowly, a small subset can progress rapidly to deeply invasive melanoma. A careful clinical exam—which Nehal described in detail—is necessary given a background of photo damage and freckling. Valuable tools include Wood's light, dermoscopy, and reflectance confocal microscopy. ***Biopsy:*** The goal is to confirm diagnosis and identify invasion that may upstage and change management. Nehal explained why it is not always

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A PUBLICATION OF THE DERMATOLOGY FOUNDATION
Sponsored by
Ortho Dermatologics
A wholly owned subsidiary of Bausch Health Companies Inc.

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Published for the Dermatology Foundation by
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This issue of *Dermatology Focus* is distributed without charge through an educational grant from Ortho Dermatologics.

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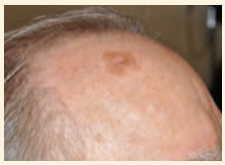
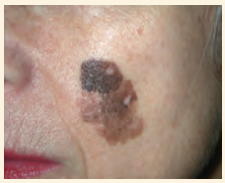
Melanoma—Lentigo Maligna Type: Management Challenges

- Natural history is variable
- Clinical/histologic presentation is variable
- Possibility of unsuspected invasion
- Possibility of unpredictable subclinical extension
- Functional vs aesthetic considerations
- **Thus management requires:**
  - Careful preoperative evaluation
  - Techniques for more exhaustive histologic margin control
  - Delay of reconstruction
  - Long-term follow-up (essential)
  - Quality of life considerations
- **Individual cases with nonsurgical management:**
  - Limited excision
  - Off-label topical imiquimod
  - Radiation
  - Observation





possible to perform a complete excisional biopsy of a large head/neck pigmented lesion, and noted alternative biopsy approaches. ***Margin control:*** "Guidelines describe clinical margins, but not how much histologic margin or clearance is sufficient." Nehal discussed her group's rationale and approach to exhaustive margin control, which centers on radial sectioning. "In our experience, the mean surgical margin for an *in situ* LM is ~7 mm, and approximately 1 cm for invasive LM." ***Reconstruction:*** Wait until you are comfortable with your margin control. ***Long-term follow-up:*** Local LM recurrence may take 5–10 years to occur, especially impactful for younger patients. ***Health-related QOL:*** Nehal discussed treatment considerations for geriatric patients vs patients <60s, including nonsurgical options, eg, off-label use of imiquimod.

Guidelines. See the 2019 JAAD guidelines (jaad. org/article/S0190-9622(18)32588-X/fulltext), and the NCCN guidelines. Use the AJCC staging system (the 8th edition released in January 2018). A helpful reference is *Lentigo Maligna Melanoma: Challenges in Diagnosis and Management*. Eds: Nehal KS, Busam KJ. Springer International Publ, 2017.

Update on Systemic Agents for Keratinocyte Carcinoma

Sarah T. Arron, MD, PhD

Introduction. Systemic treatment for basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) has emerged within the past 5 years, enabled by continued progress in molecular biology. It addresses distant metastatic and locally advanced tumors that cannot be surgically excised. Locally advanced (la) includes tumors for which surgery and/or radiation either would not be curative or would involve significant morbidity. Dr. Arron noted the importance for dermatologists of understanding the full range of systemic treatments for these inoperable cutaneous carcinomas. Patients often present initially to dermatologists, who may manage them independently or in collaboration with oncology.

Keratinocyte Carcinoma: Systemic Therapy

- For treating locally advanced* or distant metastatic tumors
- Regional/nodal metastases can often be treated with surgery and radiation without systemic therapy
- Currently no data on postoperative adjuvant therapy for KC
- **Locally Advanced (la)*: describing a tumor that either could not be cured by surgery or radiation, or for which surgery would involve significant morbidity (ie, loss of eye/ear/limb/facial nerve function). Thus the definition varies depending on tumor, patient, and access-to-care issues

cSCC. Arron described the traditional treatment approaches and their drawbacks, then the recent "revolution in systemic management." The EGFR inhibitors previously FDA-approved for SCC of the head and neck have had debatable efficacy against cSCC. "The groundbreaking change" involves checkpoint-inhibitor immunotherapy. Arron provided efficacy data for the PD-1 inhibitor *cemiplimab*, approved by the FDA in 2018 and now referenced in the 2019 guidelines as first-line therapy for metastatic and laSCC. Arron showed 2 trial patients with dramatic resolution of large metastases on the scalp. Although cemiplimab is clinically similar to the more familiar nivolumab and pembrolizumab, more time is needed to determine the degree of its immune-related adverse effects. (Question patients regularly for warning symptoms.) Although transplant recipients are more prone to developing keratinocyte carcinomas, their need to maintain immunosuppression makes immunotherapy an unlikely option. Arron summarized non-immunostimulatory systemic options.

BCC. The 2 FDA-approved systemic treatments for metastatic and laBCC—vismodegib and sonidegib—inhibit the hedgehog (Hh) signaling pathway. (Either of two Hh mutations cause 90% of BCC.) Arron highlighted the "fabulous story of science" from the academic discovery of this critical regulatory pathway in *Drosophila* embryogenesis decades ago to understanding and treating its powerful impact in human disease. She presented published response rate data, described her trial combining vismodegib with radiation, and noted her positive proof-of-concept trial for its preoperative adjuvant use.

Systemic Agents for cSCC

- Chemotherapy: cisplatin, 5-fluorouracil
- Molecular therapy: EGFR inhibition
  - Monoclonal antibodies: cetuximab, panitumumab
  - Tyrosine kinase inhibitors: erlotinib, gefitinib
- Emerging: Immunotherapy/checkpoint inhibition
  - Cemiplimab: first FDA-approved anti-PD-1 for metastatic and laCSCC
  - Other anti-PD-1/PD-L1 inibitors: nivolumab, pembrolizumab, avelumab, atezolizumab
  - In solid organ transplant recipients, potential benefit of this enabled anti-tumor immune response has to be weighed against significant risk of organ rejection

Response Rates in Context

- Hedgehog pathway inhibitors: 15–30% response rate for mBCC, 45% for laBCC
- EGFR inhibition: <18% response rate for m/laCSCC
- Cemiplimab: 50% response rate for mSCC
- Systemics should not replace first-line surgery and radiation in patients who have curable tumors without extensive communication beforehand

Bisphosphonates and Protecting Bone in Patients Taking Systemic Glucocorticoids

Janet Schlechte, MD

Introduction. Systemic glucocorticoids (GCs) are an essential therapy in a range of conditions treated by dermatologists. Osteoporosis is a potential side effect of concern. Dr. Schlechte provided guidance for understanding, identifying, and minimizing this risk.

Guidance. The most important point is to consider the potential for GC-related loss of bone density early because it occurs very rapidly, within the first few months of therapy. The second essential is to use the DEXA score and the patient's risk factors for deciding when and how to treat. Schlechte explained that GCs decrease calcium absorption, bone formation, and muscle mass, and that risk assessment combined with DEXA scans (T-score specifically in the hip and spine) can help identify candidates for therapy. Bisphosphonates are a good choice for initiating therapy and have been shown to decrease hip and spine fractures by 40%-60%. They are very well tolerated when used appropriately. Schlechte discussed the issues in stopping bisphosphonate therapy if GC therapy can be discontinued. She also emphasized the importance of maintaining gonadal function in patients who will require long-term GC therapy.

Take-home points. Remember that bone loss is most prominent during the first few months of GC therapy, and thus preventive measures must be introduced without delay. Use both T-score and risk factors in assessing the need for pharmacologic therapy.

(Continued on page 6)

New DF President's Commitment: *Helping Dermatology Be the Best It Can Be*

Janet A. Fairley, MD, John S. Strauss Professor and Chair of the Department of Dermatology at the University of Iowa, was enthusiastically welcomed as the Foundation's new president earlier this year by the Board of Trustees. A leading investigator and clinical expert in autoimmune blistering diseases and active in the Interdisciplinary Graduate Program in Translational Biomedicine, Dr. Fairley has always been deeply committed to "translating findings from the laboratory into improved diagnostics and therapies for patients." This has been her unwavering goal since her post-doc research at the University of Michigan and early-career appointments at the University of Michigan and then the University of Rochester. Before coming to Iowa in 2007, Dr. Fairley spent 17 years at the Medical College of Wisconsin where she became professor of dermatology and technical supervisor of the immunodermatology laboratories.

Dr. Fairley's new role with the DF embodies her long-term dedication to helping the specialty be the best it can be. She joined the DF over 30 years ago, recognizing that its mission is central to advancing the specialty and patient care. She is an Annenberg Circle Sustaining member, and has held several volunteer leadership roles in the annual Leaders Society campaign and the DF Medical & Scientific Committee. In recent years, she has served on the Executive Committee and co-chairs the highly regarded DF Clinical Symposia.

As the new DF president starting in a time of economic and political uncertainty, Dr. Fairley shares her perspective and goals for the Foundation.

What impact do you believe the DF has had on the specialty?

A tremendous impact. Look at clinical care today. For over 50 years, the DF's support of thoughtfully selected early research has jump-started the careers of countless investigators whose insightful discoveries and progress have profoundly advanced every aspect of our specialty.

What challenges do you see ahead confronting continued progress in the specialty?

Funding! Public funding from the NIH is very tight—as is support for patient-centered research. Emerging investigators will require early-career research dollars from the DF more than ever. Our ability to meet this need will rely more and more on the annual commitment and generosity of our colleagues. **As dermatologists, we are the only people we can count on to support our specialty and ensure that the investigators capable of producing tomorrow's advances in patient care are able to do so.**

What do you wish to accomplish as president?

I want to get the message out to every dermatologist that membership in the Dermatology Foundation is a priceless investment in the future of our specialty. I can't emphasize this strongly enough. The DF's influence on the clinical care of our patients is substantial and has enabled, for example, advances in understanding the pathology and treatments that now help our patients with psoriasis and atopic dermatitis live normal lives. This kind of clinical progress will continue—as long as we have sufficient funds to support the early research of promising investigators with the ability to make advances in the treatment of diseases that continue to challenge us.

What do you wish to say to dermatologists who are not DF members?

The Foundation is unique among the organizations serving our specialty. It is the only dermatology organization whose sole purpose is to identify people and ideas that are really going to carry our specialty forward—and then fund that research so that its potential will be realized. This has been fundamental to the level of care they give their patients. I invite them to join their colleagues in supporting significant clinical progress for the future.

How does the DF affect the individual dermatologist's experience?

Every dermatologist who is beginning their career does not want to be practicing the same medicine at the end of their career as they were at the beginning. The DF is critical to our collective future. It has continuously supported promising investigators who have brought us new knowledge and better tools—enabling us to provide progressively better care to our patients. **These innovators need our support—because not moving forward is not acceptable.** ■

Bisphosphonates decrease fracture risk, and can be stopped when GC therapy is no longer necessary. Maintain normal calcium and vitamin D levels, adequate gonadal function, and exercise. The same guidance applies to male and female patients.

Glucocorticoid-induced Bone Loss

- Risk factors: smoking, eating disorder, age, previous fracture, alcohol
- Most prominent in first months of therapy
- Limit dose and duration of steroid therapy
- Use topical or inhaled steroid if possible
- Encourage exercise; avoid ETOH/smoking

Take-home Points

- Use T-score *and* risk factors in assessing need for pharmacologic therapy; FRAX tool helpful in some cases
- Bisphosphonates decrease fracture risk
- Maintain normal calcium, vitamin D, gonadal function, and exercise

Practical Approaches to Treatment of Hyperpigmentation

Andrew F. Alexis, MD, MPH

Introduction. Hyperpigmentation is both highly common and challenging, "particularly for our patients with darker skin types," Dr. Alexis pointed out. In addition to post-inflammatory hyperpigmentation (PIH)—the most common form—there are primary disorders (eg, melasma), complications of oral drugs or harsh external irritants, and post-procedure responses (especially from laser- and light-based therapies in darker skin). Alexis offered practical treatment approaches, touching on emerging therapies and providing trial data, and shared examples from his practice.

Treatment Considerations

- How long to use topical hydroquinone?
  - 6 months continuous use, then taper or discontinue
  - No longer than 1 year of treatment
  - Non-hydroquinone product for long-term maintenance
- What are alternatives to hydroquinone?
  - Rx therapies:
    - Topical retinoids
    - Topical azelaic acid
    - Oral tranexamic acid (may modulate the vascular component of melasma)
  - Non-Rx therapies:
    - Topical cosmeceuticals with skin-brightening ingredients
    - Oral *Polypodium leucotomus* (an adjunct treatment)
- What to do if insufficient improvement with topical agents?
  - Chemical peels
  - Microdermabrasion
  - Microneedling
  - Laser/light-based device

Recommended Approaches in Skin of Color For:

- **Chemical Peels**
  - Superficial peeling agents (especially salicylic acid and glycolic acid)
  - Discontinue retinoids 1 week prior to peel
  - Query patient about exfoliative treatments done elsewhere
  - **Start low, work up slowly**
  - **Monitor patient during procedure!**
- **Lasers and light-based treatments for melasma/hyperpigmentation**
  - **Nonablative fractional lasers – SPT I-VI**
  - Low fluence quality (Q-switched 1064 nm Nd:YAG) – SPT I-V
  - Intense pulsed light – SPT I-III/IV
  - Picosecond 755 nm laser with diffractive array – SPT I-VI

Treatment options. Multiple strategies address hyperpigmentation: blocking tyrosinase, the enzyme that catalyzes melanin production in melanosomes (with hydroquinone, licorice extract, azelaic acid, kojic acid); blocking melanin transfer from melanocyte to keratinocyte (with topical retinoids, a soy trypsin inhibitor, niacinamide); blocking the secretory function of melanocytes (corticosteroids); and removing existing excess melanin (chemical peels, retinoids). "Our primary strategy is hydroquinone 4% (combined with tretinoin and fluocinolone), as it is very reproducible and efficacious." Alexis addressed its benefits and limitations, including the risks of exogenous ochronosis when used long term. Topical alternatives involve both prescription agents (including retinoids and azelaic acid) and the growing list of skin-lightening cosmeceuticals. The best of the topical alternatives are almost comparable to 4% hydroquinone, and hold value for adjunctive or sequential use with hydroquinone and for long-term maintenance afterward. Address still-persistent hyperpigmentation—especially dermal pigmentation—with office procedures (nonablative lasers and light-based therapies), "used with caution." Alexis specified the safest nonablative lasers and usage guidelines for darker skin types. He noted data for microneedling, and the oral tranexamic acid for melasma.

In summary. "When faced with hyperpigmentation, I start with hydroquinone 4%. For recalcitrant cases, I may try compounded

hydroquinone >4%. One of the non-hydroquinone agents or cosmeceuticals can be combined for added benefit, or introduced when transitioning off hydroquinone after 6 months. Cases that still persist can be treated with in-office procedures and possible adjunctive agents. Throughout, emphasize comprehensive sun protection."

+/- Chemical peels, laser, microneedling, oral agents

≤6 months

- Hydroquinone 4% (triple combination formulation preferred)
- Consider higher concentrations
- Severe/recalcitrant cases

≥6 months

- Non-hydroquinone agent
  - Azelaic acid
  - Topical retinoids
  - Kojic acid
  - Other cosmeceuticals

Broad spectrum sunscreen (SPF 30 or higher)
Cover-up cosmetics

MINI-SYMPOSIUM: DIAGNOSTIC DILEMMAS IN ADULT AND PEDIATRIC DERMATOLOGY

Patch Test Challenges

Mark D. P. Davis, MD

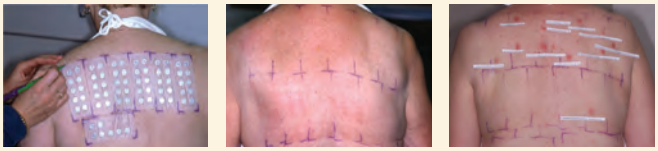
The challenges. Dr. Davis discussed the basic challenges in searching for the culprit responsible for a persistent rash. ***One:*** When to patch test? Do it with any type of dermatitis, as the culprit may be a contributor if not the primary cause. ***Two:*** How is it done? Davis advised beginning with one of the numerous standard series. The TRUE Test is especially popular because of its pronounced ease of application. Also patch test to the specific products the patient applies and leaves on the skin. Add a specialty series if they are available. ***Three:*** Teach the patient how to avoid the identified allergens and provide resources for finding replacement products (see below). ***Four:*** "There are controversies surrounding almost everything I've discussed here."

Sleuthing. Davis presented 11 illustrative patients. For each one, he traced the clues and thinking that led to identification of the respective culprit and distilled the lessons to be learned. And for the patient who steadfastly fails to improve regardless of diagnoses and treatments, "consider patch testing to topical steroids."

Resources. Two websites help patients find skin care products to replace the ones they must now avoid. CAMP (Contact Allergen Management Program), developed by the American Contact Dermatitis Society, is free to members: https://www.contactderm.org/resources/acds-camp. SkinSAFE is a commercial fee-based service (https://www.skinsafeproducts.com). For non–skin care products: A. Scheman et al. "Contact allergy: Alternatives for the 2007 North American Contact Dermatitis Group (NACDG) Standard Screening Tray." *Dis Mon*. 2008;54:7–156.

Where Should I Start?

- Very few allergens have been FDA-approved, which is why the companies manufacturing them are based outside the U.S.
- Standard series—the "starting point" for almost all patch testing
- But which standard?
  - ACDS core allergens
  - North American
  - NACDG
  - TRUE test
  - Mayo
  - European
  - Italian
  - Portuguese
- Examples of specialty series
  - Rubber series
  - Corticosteroid series
  - Plastics and glues series
- Patient's own products



Practical Pedi Derm Diagnoses That Can Stump the Adult Dermatologist

Sheilagh M. Maguiness, MD

Introduction. Dr. Maguiness discussed 5 patients presenting problems that can stump dermatologists who do not regularly encounter them.

The stumpers. ***Toilet seat dermatitis (TSD):*** This 4-year-old girl had experienced several months of oozy, itchy skin isolated to her buttocks and thighs—"a classic example of TSD." The wood, plastic, and seat-cleaning products contain multiple allergenic/irritant compounds. This very common cause of contact dermatitis in children—especially toddlers who are toilet training—is "typically under-recognized," in part because its features can vary and it may induce "Id" reactions that mimic generalized AD. Avoid contact (paper seat covers are one solution) and harsh cleaners. Treat much like basic AD—restore the skin barrier, address inflammation and secondary bacterial colonization. ***Slime dermatitis:*** A 9-year-old girl's itchy rash of several months had spread from her palms to her shoulders and legs. Maguiness learned that her hobby was making play "slime"—typically including a minimum of borax, adhesive glue, and contact lens solution—which can cause allergic and irritant contact dermatitis.

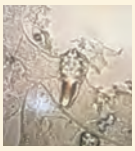
Toilet Seat Dermatitis

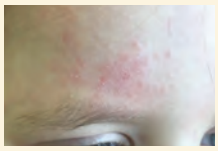
- Common cause of contact dermatitis with toilet training
- May present with eczematous plaques and impetiginization on the posterior thighs
- Id reactions are common
- Etiology unclear—suspected combination of harsh cleaners & allergens
- **To treat:**
  - Avoid contact: raise seat or cover it (paper, fabric)
  - Avoid harsh cleansing agents: use soapy water, dilute bleach, or vinegar/water
  - Skin barrier repair: daily soaking bath; thick emollient (eg, Vaseline®, Aquaphor®)
  - Identify and treat superinfection; daily dilute bleach baths are *very helpful*
  - Topical steroids—mid- to-moderate strength—are necessary: mometasone ointment bid for ≤2 weeks, then step down to lower potency

Idiopathic facial aseptic granuloma: A 2-year-old girl with a large violaceous fluctuant nodule on her right cheek (not tender or pruritic) also had recurrent eyelid papules and chalazia. Maguiness discussed the variants of this uniquely pediatric entity, thoughts about etiology, possible co-existence with perioral dermatitis, and the diagnostic value of ultrasound vs biopsy. Many cases resolve spontaneously. ***Demodex dermatitis:*** A 4-year-old girl on maintenance chemotherapy for pre-B cell acute lymphoblastic leukemia had a 3-month history of an extremely itchy rash on her cheeks and forehead. Scraping revealed demodex, normally rare prepubertally but more common in the immunocompromised. Treatments include topical permethrin, oral or topical ivermectin. ***Congenital hemangioma (CH):*** The vascular-appearing nodule noted the day after birth on the anterior neck of this 2-week-old female had already been evaluated for a suspected tumor. When Maguiness used a simple Doppler US, the turbulent "whoosh" sound indicated intra-lesional high blood flow. Being both high-flow and fully formed at birth facilitated a diagnosis of CH. (Office-based Doppler US helps narrow the diagnosis for similar lesions, avoiding more extensive/invasive imaging.) CH—rare vascular tumors—are distinct from infantile hemangiomas. Maguiness discussed their presentation, subtypes, and potential complications. Active intervention is rarely necessary.

Demodex: Acneiform Eruptions and Perioral Disease

- Well-described in immunocompromised children
- Scrapings will demonstrate the mites
- Treatment with oral and/or topical ivermectin





Congenital Hemangiomas (CH)

- These rare vascular tumors are distinct from infantile hemangiomas and present fully formed at birth
- There are 3 well-described subtypes:
  - RICH—rapidly involuting congenital hemangioma
  - NICH—non-involuting congenital hemangioma
  - PICH—partially involuting congenital hemangioma
- CH can mimic other tumors, and thus may prompt unnecessary imaging or workup
- In most cases, active intervention is not necessary

Hot Topics in Pediatric Infectious Diseases

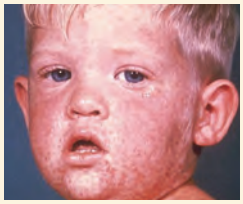
Vikash S. Oza, MD

Introduction. Dr. Oza touched on several issues requiring an updated perspective. Measles has resurfaced. The classic viral exanthem hand, foot, and mouth disease (HFMD) has changed its face. And we continue to struggle with MRSA infection.

Updates. ***Measles:*** Initially a re-emerging concern in NYC, it is now spreading across the U.S. Thus a child coming in with a morbilliform rash and fever connotes a broad differential that, once again, includes measles. Oza reviewed his NYC epidemic experience, then provided a brief primer. "We worry because it's one of the most infectious viruses there is, and measles can have serious systemic consequences, including pneumonia, encephalitis, and prolonged immunosupression." Dermatologists should remain vigilant and strongly consider measles in children who are unvaccinated, immunosuppressed, or have recently traveled to an outbreak area. ***HFMD:*** In the U.S., coxsackievirus A6 has become the most predominant viral strain causing HFMD, with a more varied clinical presentation. Oza described features vulnerable to misdiagnosis, including a unique distribution around the mouth that can be mistaken for impetigo. The patient is not systemically ill, so supportive care is sufficient. The family should anticipate some hand and foot peeling (within 1–2 weeks) and possible nail shedding (in several months). ***MRSA:*** Oza described a severely ill patient who remained a puzzle until histopathology found MRSA in the deep dermis. Then he discussed the challenges of a Staph strain in Brooklyn that has become resistant to mupirocin ointment and chlorhexidine. He pointed out that colonization in young children is typically located around the perirectal area, which can lead to recurrent abscesses, folliculitis, or impetigo. Oza rarely uses mupirocin in managing his AD patients because of concern for acquiring resistance. "It all comes back to antibiotic stewardship."

Measles

- What is our role?
  - Identify
  - Isolate (airborne precautions)
  - Report to Department of Public Health
- Biologic therapy and live virus vaccines
  - Current guidelines: no live vaccines while on biologic therapies and for at least 6 months after
  - *Consult Infectious Disease* for high-risk patients during an outbreak



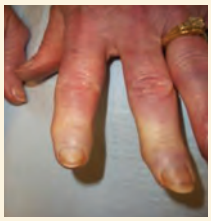
Take-home points. We must retain measles in our differential diagnosis, especially for people who visited areas where it is endemic. Know that enterovirus infections change, and that HFMD looks completely different now in 2019. We need to remain aware of topical antibiotic resistance in *Staphylococcus* species.

Distinguishing Sclerosing Diseases

Nicole Fett, MD, MSCE

Introduction. Dr. Fett provided guidance for distinguishing patients with morphea from limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis (the 2 main types of systemic sclerosis seen by dermatologists) and from eosinophilic fasciitis (EF). She also illustrated the differences between limited and diffuse systemic sclerosis. Then she outlined her approach to patients with morphea.

Systemic Sclerosis: Making the Diagnosis



+ ANA

- + anti-centromere

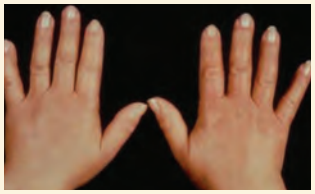
OR

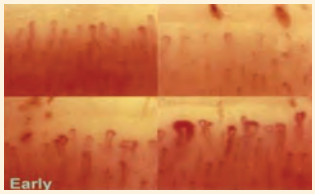
- + anti-Scl-70

OR

- + anti-RNA polymerase

OR



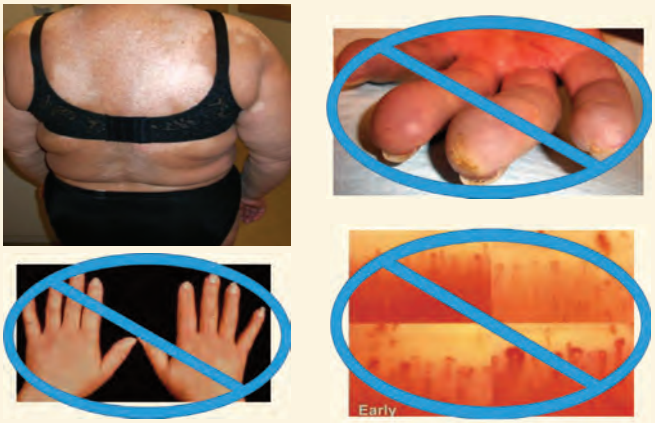


T. Minier et al. *Ann Rheum Dis.* 2014;73:2087–93.

The differences. *Both limited and diffuse* cutaneous systemic sclerosis involve similar changes, with the names reflecting their differing degree of cutaneous involvement. ***Systemic sclerosis:*** skin changes are contiguous and spread distal to proximal. Hand changes are characteristic—redness and puffiness, sclerodactyly (finger skin that is immobile when pinched), digital ulcers, and pitting are common, and nailfold capillary dilation is expected. Most patients also have Raynaud's phenomenon. Facial tightening occurs, with decreased oral aperture and mat-like telangiectasias. Most patients are ANA-positive, and ~50% also have a systemic sclerosis–specific antibody. ***Morphea:*** skin changes are patchy, discontiguous, and do not follow a distal-to-proximal spread. There are no hand changes (with the exception of linear morphea). Raynaud's phenomenon prevalence reflects that of the normal population. Facial involvement is rare except in linear morphea, which is linear and unilateral. Many patients are ANA-positive, but have no systemic sclerosis–specific antibodies. ***EF:*** Fett described the ways in which EF is distinctive.

Morphea patients. Fett discussed evaluation, support, and treatment decision points. "When I am evaluating a patient for morphea, my concerns are: (1) Is there still active disease that I can treat with immunosuppression? (2) Is there disease damage that I can get consults to help with? (3) Can I help with the patient's emotional response to their chronic disease?" She stressed the need to assess mucous membranes, including the mouth and genitals. It is very common for patients with morphea to develop lichen sclerosus of these membranes, which—if not treated—increases the risk of squamous cell carcinoma.

Morphea: Making the Diagnosis



T. Minier et al. *Ann Rheum Dis.* 2014;73:2087–93.

Approach to the Patient with Morphea

- History of present illness
  - Is the patient developing new spots?
  - Is there expansion of existing spots?
  - Symptoms of pain/itch?
  - Functional limitations?
  - Emotional limitations?
- Additional history
  - Past medical history—autoimmune disease?
  - Family history—autoimmune disease?
  - Social history: alcohol/injectable drug use?
- Labs?
  - Currently none recommended—with exception of prepping for MTX or ruling out concomitant autoimmune disease based on history and exam
- Biopsy—only if not a classic presentation
- Consults?
  - Opthalmology (if child with head and neck); PT/OT/Ortho
- Treatment decision points:
  - Subtype
  - Depth of involvement
  - Disease activity

MINI-SYMPOSIUM: MEDICAL DERMATOLOGY

Pyoderma Gangrenosum

Misha A. Rosenbach, MD

Introduction. Dr. Rosenbach focused on recognizing and correctly diagnosing the rare and poorly understood neutrophilic dermatosis pyoderma gangrenosum (PG), emphasizing the dermatologist's unique and clarifying contributions. He also discussed the need to evaluate patients for the systemic diseases likely to be associated with PG, as they also require treatment, then outlined the treatment approach and options for PG.

Recognizing and diagnosing PG. Of the 5 subtypes, Rosenbach focused on *ulcerative* disease as this is what most patients have. He profusely illustrated the distinctive dermal ulcers with violaceous, overhanging, and highly inflamed borders, substantial edema and purulence—all reflecting an active neutrophilic inflammation. Although a diagnosis requires both major criteria and 2 minor ones, in reality most patients have them all. The *major* criteria are (1) *rapid* progression of a painful cutaneous ulcer with an irregular, undermined, violaceous border, and (2) all other possibilities have been ruled out. The *minor* criteria include *pathergy* (development/worsening of lesions at sites of trauma), cribriform scarring, histologic features consistent with PG, associated systemic disease, and an appropriate response to treatment. Rosenbach discussed pathergy and associated systemic diseases extensively. He described the proper biopsy and its importance.

Pyoderma Gangrenosum

Proposed diagnostic criteria: Both major + at least 2 minor

- Major criteria
  - Rapid progression of a painful cutaneous ulcer with an irregular, violaceous, undermined border
  - Other causes of cutaneous ulceration have been excluded
- Minor criteria
  - History suggestive of pathergy or cribriform scarring
  - Systemic diseases associated with PG
  - Histopathologic findings
  - Treatment response

Managing a Patient with PG

- Evaluation
  - Thorough history (Rx's), physical, ROS
  - Labs, imaging, testing guided by H&P, demographics
  - CBC, CMP
    - ANA, ANCA, SPEP
    - GI studies
  - Biopsy in (almost) all cases (+ culture)
- Treatment
  - Step 1: Stop the inflammation—systemic and local meds
    - "Rapid response": pain, exudate, edema/erythema less within 1 week
  - Step 2: Heal the wound—depends on other factors
    - Local ulcer management, supportive care

Most patients with PG have an ***associated systemic disease.*** Rosenbach detailed the evaluation requirements. Inflammatory bowel disease (IBD) is most common, regardless of age. Inflammatory arthritis, malignancy, and hematologic disorders are more common in older patients than younger ones. PG ***treatment*** comprises two distinct, sequential goals. "Step 1 is stopping the neutrophilic inflammation driving the ulcer, an acute and rapid process. Then step 2 is to gradually heal the wound." Step 1 is rapid; step 2 can take months to years depending on the ulcer site and size. For step 1, Rosenbach discussed prednisone, cyclosporine, and the TNF-α inhibitor infliximab (best for the PG patient with IBD, as it treats both). He also discussed the dermatologist's vital contribution in identifying and treating complicating factors that can impair healing.

Take-home points. Once you are confident in your diagnosis, *do not overtreat*. Use immunosuppressive medication to stop the inflammation, and then heal the wound.

Dermatomyositis and Mimics

Nicole Fett, MD

Introduction. Dr. Fett provided the most current information needed to recognize, understand, and treat the different DM phenotypes. She liberally illustrated her talk with clinical photos.

Clarifying DM. Fett began with the more recently recognized DM subgroup, *amyopathic DM*: patients with characteristic cutaneous disease and risk for both interstitial lung disease and malignancy, but who do not develop myositis. This entity has now been accepted by the rheumatology community, and patients can be enrolled in clinical trials. Fett described the profile of classic cutaneous features for DM, including, among others, the heliotrope rash and other distinctive facial manifestations, V-neck and shawl erythema, Gottron's sign and papules, poikiloderma patches, nailfold changes, mechanic's hands, holster sign, and full-field erythema of the scalp. Calcinosis is more common in children. ***Antibodies*** "can tell us about the patient's underlying risk for systemic disease." Fett profiled 6 autoantibodies, indicating the normal function of the disrupted protein along with the associated phenotype and particular risks. She discussed the ***cutaneous differential***—hydroxyurea-induced dermatomyositis, acute cutaneous lupus, psoriasis, and multicentric reticulohistiocytosis—with detailed guidance on the telltale differences.

Treatment. "It is important to think beyond the skin, and about how the treatments we are choosing also affect the patient's muscles and lungs." Fett detailed the elements for treating mild DM without myositis, then indicated which agents to use for more severe cutaneous disease, agents that also treat myositis, and agents that are effective and safe for those patients with interstitial lung disease (methotrexate is typically avoided, with emphasis on mycophenolate mofetil and, increasingly, IVIG).

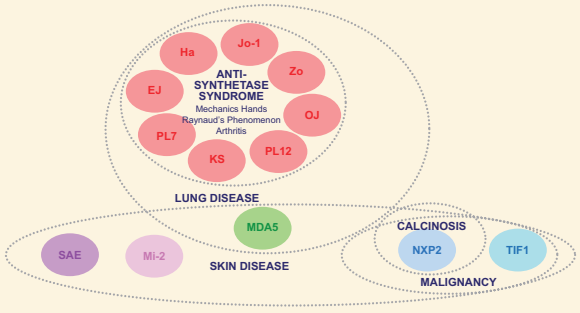
Dermatomyositis: Cutaneous Features

- Facial erythema that includes the nasolabial folds
- Heliotrope sign
- Gottron's sign
- Gottron's papules
- Mechanic's hands
- Ragged cuticles
- Nailfold capillary dilation and hemorrhage
- V-neck erythema
- Shawl sign
- Poikiloderma
- Holster sign
- Band of involvement on the low back
- Calcinosis
- Ulcerations

Cutaneous Differential

- Hydroxyurea-induced dermatomyositis
- Acute cutaneous lupus
- Psoriasis
- Multicentric reticulohistiocytosis
- Ulcerations

Dermatomyositis Antibody-phenotype Associations



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(Continued on page 13)

For adults with plaque psoriasis

bettertogether

The first and only steroid/retinoid therapy, allowing **halobetasol** and **tazarotene** to work together in an advanced, once-daily lotion that can be dosed to clearance[1-3]

DUOBRII™
(halobetasol propionate and tazarotene)
Lotion 0.01% / 0.045%

mechanisms of change

Halobetasol (0.01%)

Provides powerful antiinflammatory effects and reduces skin irritation, which is often associated with retinoids[1,4,5]

Tazarotene (0.045%)

Regulates cell growth and specialization to reduce hyperproliferation, increases collagen, and extends remission post treatment[4,6,7]

The only FDA-approved treatment with a potent-to-superpotent steroid that can be used until control is achieved

The efficacy and safety of DUOBRII Lotion was investigated in two 8-week clinical trials and an additional 1 year safety study.[1,3]
Discontinue treatment with DUOBRII Lotion when control is achieved or if atrophy, striae, telangiectasias, or folliculitis occurs.[1]

American Academy of Dermatology (AAD) Guidelines give the combination of a corticosteroid and a retinoid an A rating with Evidence Level I for the treatment of psoriasis[4]

Indication

DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%, is indicated for the topical treatment of plaque psoriasis in adults.

Important Safety Information

Contraindication

DUOBRII Lotion is contraindicated in pregnancy.

Warnings and Precautions

- Women of child-bearing potential should be warned of the potential risk of fetal harm from DUOBRII and use adequate birth-control. A negative result for pregnancy should be obtained within 2 weeks prior to treatment. If the patient becomes pregnant during treatment, discontinue DUOBRII Lotion and advise patient of the potential hazard to the fetus.
- DUOBRII Lotion has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis during or after treatment and may require that patients be evaluated periodically during treatment.
- Predisposing factors for HPA axis suppression include: use of more potent corticosteroids, use on large areas, use under occlusive dressings, use on altered skin barrier, concomitant use of other steroids, liver failure and young age.
- Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria.
- Local adverse reactions may include atrophy, striae, telangiectasias, folliculitis and contact dermatitis. If these effects occur, discontinue until the integrity of the skin has been restored. Do not resume treatment if contact dermatitis is identified. DUOBRII Lotion should not be used on eczematous skin, as it may cause severe irritation.
- Avoid exposure to sunlight, sunlamps and weather extremes. Patients with sunburn should be advised not to use DUOBRII Lotion until fully recovered. DUOBRII Lotion should be administered with caution if the patient is also taking drugs known to be photosensitizers because of the increased potential for photosensitivity.
- Topical corticosteroids may increase the risk of cataracts and glaucoma; advise patients to report any visual symptoms and refer to an ophthalmologist if needed.

Adverse Events

- The most common adverse events in clinical trials were contact dermatitis (7%), application site pain (3%), folliculitis (2%), skin atrophy (2%), and excoriation (2%).

To report SUSPECTED ADVERSE REACTIONS, contact Ortho Dermatologics at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.

Please see Brief Summary of full Prescribing Information on the following page.

References **1.** DUOBRII Lotion [prescribing information]. Bridgewater, NJ: Bausch Health US, LLC. **2.** Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed April 29, 2019. **3.** Data on file. **4.** Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 2009;60(4):643-659. **5.** Orfanos CE, Schmidt HW, Mahrle G, et al. Retinoic acid in psoriasis: its value for topical therapy with and without corticosteroids: clinical, histological and electron microscopical studies on forty-four hospitalized patients with extensive psoriasis. *Br J Dermatol*. 1973;88(2):167-182. **6.** Lesnik RH, Mezick JA, Capetola R, Kligman LH. Topical all-trans-retinoic acid prevents corticosteroid-induced skin atrophy without abrogating the anti-inflammatory effect. *J Am Acad Dermatol*. 1989;21(2 Pt 1):186-190. **7.** Weinstein GD, Krueger GG, Lowe NJ, et al. Tazarotene gel, a new retinoid, for topical therapy of psoriasis: vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. *J Am Acad Dermatol*. 1997;37(1):85-92.

Learn more at DUOBRII.com

Ortho | Dermatologics

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe DUOBRII safely and effectively. See full Prescribing Information for DUOBRII.

DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% for topical use

INDICATIONS AND USAGE

DUOBRII (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% is indicated for the topical treatment of plaque psoriasis in adults.

CONTRAINDICATIONS

Pregnancy

DUOBRII Lotion is contraindicated in pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Embryofetal Risk

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, DUOBRII Lotion may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Tazarotene is teratogenic, and it is not known what level of exposure is required for teratogenicity in humans *[see Contraindications and Clinical Pharmacology]*. Tazarotene elicits teratogenic and developmental effects associated with retinoids after topical or systemic administration in rats and rabbits *[see Use in Specific Populations]*.

Advise pregnant females of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to DUOBRII Lotion therapy. Initiate DUOBRII Lotion therapy during a menstrual period. Advise females of reproductive potential to use effective contraception during treatment with DUOBRII Lotion therapy *[see Use in Specific Populations]*.

Hypothalamic–Pituitary–Adrenal (HPA) Axis Suppression and Other Unwanted Systemic Glucocorticoid Effects

DUOBRII Lotion contains halobetasol propionate, a corticosteroid, and has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Systemic effects of topical corticosteroids may include reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment of the topical corticosteroid.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with DUOBRII Lotion was evaluated in a study of 20 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area. The subjects were treated once daily for 8 weeks and assessed for HPA axis suppression at Weeks 4 and 8. HPA axis suppression occurred in 3 out of 20 (15%) subjects at Week 4 and none (0%) of these 20 subjects had HPA axis suppression at Week 8 *[see Clinical Pharmacology in full Prescribing Information]*.

Because of the potential for systemic absorption, use of topical corticosteroids, including DUOBRII Lotion, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age. An adrenocorticotropic hormone (ACTH) stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug or reduce the frequency of application. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to topical corticosteroids. Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids because of their larger surface-to-body mass ratio *[see Use in Specific Populations]*.

Local Adverse Reactions

Local adverse reactions may include atrophy, striae, telangiectasias, folliculitis and contact dermatitis. Some local adverse reactions may be irreversible. If these adverse reactions occur, discontinue the medication at least until the integrity of the skin is restored; do not resume treatment if allergic contact dermatitis is identified.

Avoid use of DUOBRII Lotion on eczematous skin, as it may cause severe irritation.

Photosensitivity and Risk for Sunburn

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of DUOBRII Lotion. Patients must be instructed to use sunscreens and protective clothing when using DUOBRII Lotion. Patients with sunburn should be advised not to use DUOBRII Lotion until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using DUOBRII Lotion.

DUOBRII Lotion should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Ophthalmic Adverse Reactions

Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. Cataracts and glaucoma have been reported postmarketing with the use of topical corticosteroid products. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

Concomitant Skin Infections

Use an appropriate antimicrobial agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of DUOBRII Lotion until the infection has been adequately treated.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In randomized, double-blind, multicenter, vehicle-controlled clinical trials, 410 adults with plaque psoriasis were treated with DUOBRII Lotion or vehicle lotion and had post-baseline safety data. Subjects applied DUOBRII Lotion or vehicle lotion once daily for up to eight weeks. The adverse reactions occurring in ≥1% of the subjects treated with DUOBRII through Week 8 were contact dermatitis (7%), application site pain (3%), folliculitis (2%), skin atrophy (2%), and excoriation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, DUOBRII Lotion may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Safety in pregnant females has not been established. The potential risk to the fetus outweighs the potential benefit to the mother from DUOBRII Lotion during pregnancy; therefore, DUOBRII Lotion should be discontinued as soon as pregnancy is recognized *[see Contraindications, Warnings and Precautions, Clinical Pharmacology]*.

Observational studies suggest an increased risk of low birthweight in infants with the maternal use of potent or very potent topical corticosteroids *(see Data)*.

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose 11 times the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 116 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 9 and 228 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 9 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during the period of organogenesis to pregnant rats and rabbits *(see Data)*. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of DUOBRII Lotion.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Human Data

Available observational studies in pregnant women did not identify a drug-associated risk of major birth defects, preterm delivery, or fetal mortality with the use of topical corticosteroids of any potency. However, when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the entire pregnancy, maternal use was associated with an increased risk of low birth weight in infants.

Animal Data

Halobetasol propionate has been shown to cause malformations in rats and rabbits when given orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats but not in rabbits.

In an embryofetal development study in rats, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. Reduced fetal body weights and reduced skeletal ossification occurred at this dose (11 times the MRHD based on AUC comparison). In an embryofetal development study in rabbits, a tazarotene gel formulation, 0.5%, 0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits during gestation days 6 through 18. Single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (116 times the MRHD based on AUC comparison).

When tazarotene was given orally to animals, developmental delays were seen in rats; malformations and post-implantation loss were observed in rats and rabbits at doses producing 9 and 228 times, respectively, the MRHD (based on AUC comparisons).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, classic developmental effects of retinoids including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (16 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at that dose.

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to 5 times the MRHD (based on AUC comparison).

Lactation

Risk Summary

There are no data on the presence of tazarotene, halobetasol propionate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production after treatment with DUOBRII Lotion.

After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk.

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUOBRII Lotion and any potential adverse effects on the breastfed child from DUOBRII Lotion.

Clinical Considerations

Advise breastfeeding women not to apply DUOBRII Lotion directly to the nipple and areola to avoid direct infant exposure.

Females and Males of Reproductive Potential

Pregnancy Testing

DUOBRII Lotion is contraindicated in women who are pregnant. Females of reproductive potential should be warned of the potential risk and use adequate birth-control measures during treatment with DUOBRII Lotion. The possibility that a female of reproductive potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy should be obtained within 2 weeks prior to DUOBRII Lotion therapy, which should begin during menstruation.

Contraception

Based on animal studies, DUOBRII Lotion may cause fetal harm when administered to a pregnant female *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment with DUOBRII Lotion.

Pediatric Use

Safety and effectiveness of DUOBRII Lotion in pediatric patients under the age of 18 years have not been evaluated.

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children *[see Warnings and Precautions]*.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema *[see Warnings and Precautions]*.

Geriatric Use

Of the 270 subjects exposed to DUOBRII Lotion in clinical trials, 39 subjects were 65 years or older. Clinical trials of DUOBRII Lotion did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 1.4 times the MRHD (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposure at the highest dose was 35 times the MRHD (based on AUC comparison).

Halobetasol propionate was not genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germinal and somatic cells of rodents, and in a mammalian spot test. Positive mutagenicity effects were observed in a mouse lymphoma gene mutation assay in vitro and in a Chinese hamster micronucleus test.

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in an in vivo mouse micronucleus test.

Studies in rats following oral administration of halobetasol propionate at dose levels up to 0.05 mg/kg/day, approximately 0.53 times the MRHD based on BSA comparisons, indicated no impairment of fertility or general reproductive performance.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was 5 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day tazarotene, which produced a systemic exposure 17 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose, which produced a systemic exposure 30 times the MRHD (based on AUC comparison).

Manufactured for:
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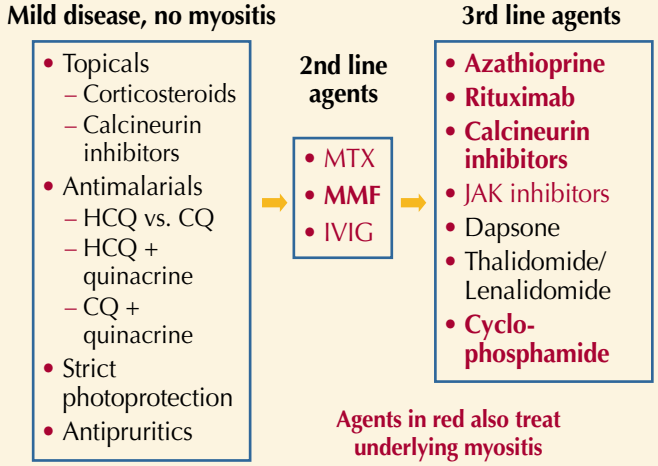
By:
Bausch Health Companies Inc.
Laval, Quebec H7L 4A8, Canada

U.S. Patent Numbers: 6,517,847; 8,809,307 and 10,251,895

DUO.0039.USA.18 Based on 9645601

Dermatomyositis Skin Disease Treatment



Adapted from A.N. Femia et al. *Am J Clin Dermatol*. 2013;14:291–313. (Reprinted with permission from Springer.)

Management of Patients Taking Glucocorticoids —Common Issues and Misconceptions

Janet Schlechte, MD

Introduction. The management of patients on long-term glucocorticoid therapy remains a challenge, especially related to perioperative steroid coverage and the use of stress doses. Dr. Schlechte reviewed conventional wisdom, which holds that 100–300 mg of hydrocortisone is needed preoperatively to prevent adrenal crisis. It has also been widely taught that a normal adrenal secretes about 30 mg of cortisol daily. But concerns about long-term replacement doses of glucocorticoids have led to re-analysis of both of these parameters. Schlechte noted more recent information pointing to daily cortisol secretion rates that are actually closer to 10 mg daily.

Current knowledge: surgical settings. The re-analysis of cortisol secretion in surgical settings has demonstrated that procedures differ markedly in how the pituitary adrenal axis will respond to stress and how cortisol production will be affected. It is clear that a simple, uncomplicated procedure will not require use of megadoses of hydrocortisone to prevent adrenal insufficiency, while a patient requiring a CABG may well require the more typical hydrocortisone dosing as noted above. In considering the need for preoperative stress doses, it is vital to consider the length of exposure to steroids, the magnitude of the stress, and the type and duration of glucocorticoid coverage,

When to Give Stress Doses, and How Much

- Consider stress magnitude and duration in determining need for higher dose
- **Significant stressors:** pneumonia, sepsis, bowel perforation
  - 50–100 mg hydrocortisone in these cases
- **Perioperative glucocorticoid coverage:**
  - Minor surgical stress–inguinal hernia
    - 25 mg HC equivalent
  - Moderate stress–colon resection
    - 50–75 mg HC equivalent
  - Major stress–CABG
    - 100–150 mg HC equivalent
- Use stress dose for the acute event only
- Monitor clinical condition to assess therapy duration
- A prolonged taper will exacerbate glucose intolerance, infection, fractures, and proximal muscle weakness

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and to use stress doses appropriately and sparingly. Using current glucocorticoid equivalencies will help avoid over-replacement.

Current knowledge: tapering. In situations where the dose can be lowered and the glucocorticoid can be tapered, start the taper as close to a physiologic dose as possible to avoid unnecessary long-term exposure to high doses. For a prolonged or difficult taper, refer to an endocrinologist.

When is the HPA Axis Suppressed?

- Minimal or no suppression
  - any dose <3 weeks
  - ≤5 mg prednisone daily
- Functional suppression
  - ≤20 mg of prednisone for >3 weeks
  - clinical Cushing's

Drug Reactions: Recent History and Evolving Landscape in SJS/TEN Management

Misha A. Rosenbach, MD

Introduction. 10% of all drug regimens produce complications. Adverse cutaneous drug reactions occur in ~2–3% of patients. About 2% of these are severe, ie, they require or prolong hospitalization or are life-threatening: SJS (Stevens-Johnson syndrome, ~5% mortality rate) and/or TEN (toxic epidermal necrolysis, ~30% mortality rate). Dr. Rosenbach described their similar presentation and initial management steps, then discussed the current uncertainties clouding drug treatment options, and reviewed emerging approaches in the dermatology community to produce accurate data.

Description and treatment. In adults, SJS/TEN are typically drug-induced and tend to occur in patients taking a larger number of medications. Causative drugs include allopurinol, carbamazepine, and sulfamethoxazole. Children can also experience infectious triggers (especially mycoplasma, though that is best thought of as mycoplasma-induced rash and mucositis—MIRM—rather than SJS). TEN is more severe with a higher mortality rate, but otherwise the two are similar. Some patients (<10%) have only SJS, 10–30% have an overlap, and >30% have only TEN. Fever and mucositis (which can become severe) are followed by rash, then by nonblanching 2-zoned targetoid lesions—erythematous with dusky centers—that produce burning pain. In SJS, ≤10% of epidermis may detach; in TEN, the rash blisters, and sheets of skin and mucosa can come off. Early identification is critical. Rosenbach described the evaluation steps for a hospitalized patient with early disease, including checking the mucosa for lesions. Following diagnosis, stop the culprit drug, transfer the patient to a high-level ICU or a burn unit, provide substantial supportive care, and bring in ophthalmology and other consults to avoid/minimize chronic damage. Rosenbach discussed burn specialists (who prefer debridement and skin grafting) vs dermatologists (leave the skin intact, as it provides the best possible dressing; keep it moist and slather with Vaseline®). Regarding therapeutic medication interventions, Rosenbach reviewed the current equivocal data and lack of consensus, and recent U.S. dermatology-based data suggesting benefit for steroids combined with IVIG. European experts overall continue to favor cyclosporine, and recent publications out of Taiwan illustrate the promise of TNF inhibitors. Research is also beginning to identify drug- and gene-specific susceptibility markers for SJS/TEN, enabling the start of preventive screening.

Conclusions. We have a number of tools to work with in managing SJS/TEN, but we have a lot more to learn. ■

SJS and TEN: Chronic Concerns

- Cutaneous
  - Dyspigmentation, nonscarring
  - Pruritus, hyperhidrosis, dryness
  - Onycholysis +/- onychodystrophy
- Mucosal
  - Urethral, esophageal, anal strictures
  - Vaginal adhesions, pruritus
  - Ocular scarring, entropion, trichiasis, sicca syndrome
  - Depapillation of the tongue impairing taste

M. Mockenhaupt. *J Invest Dermatol.* 2008;128:35–44; M. Mockenhaupt. *Expert Rev Clin Immunol.* 2011;7:803–13 .

SJS and TEN

- SJS: 1.2–6 per million person-years; ~5% mortality
- TEN: 0.4–1.2 per million person-years; ~30% mortality
- Almost always drug-induced (infectious etiology rare, although more common in kids)
  - Increased risk in elderly ← polypharmacy
  - Slight female predominance ← increased drug intake
  - Considerably increased risk in HIV, SLE, BMT
- ***Highest risk drugs:*** antibacterial sulfonamides (trimethoprim-sulfamethoxazole), anticonvulsants (carbamazepine, phenobarbital, phenytoin), oxicam NSAIDs, allopurinol
- Lamotrigine
- Nevirapine
- ***Management:***
  - Stop culprit drug
  - Transfer patient to ICU (or burn center)
  - Supportive care
  - Systemic therapy

Save the Date: Sunday, March 22—*Annual Leadership Gala*

The Dermatology Foundation's ***Annual Leadership Gala*** is a very special way to recognize members who give at a leadership level to support the early research essential for advancing patient care. The gala will honor 2019 *Leaders Society,* Annenberg Circle, *AC Sustaining,* and Fitzpatrick members. The celebration will be held from 7:30–9:00 pm at the innovative History Colorado Center. Add this special event to your calendar and enjoy the company of your colleagues in the "mile high city"!

Be sure to complete your leadership contribution by December 31 to receive your invitation for this special event.

2019 CLINICAL SYMPOSIA FACULTY
Proceedings—Part II

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2019 DF Clinical Symposia Faculty Disclosures (*Part II*)

Andrew F. Alexis, MD, MPH: Almirall, Beiersdorf, BiopharmX, Bristol-Myers Squibb, Celgene, Cipla, Dermavant, Galderma, Leo Pharma, Menlo, Novartis, Rxl, Pfizer, Sanofi-Regeneron, Trevi, Unilever, Bausch Health. **Sarah T. Arron, MD PhD:** Aspyrian, Amyris, Biossance, Castle Biosciences, Castle Creek Pharmaceuticals, Enspectra, Genentech, Genentech/Roche, Gerson Lehrman Group, Leo Pharma, Menlo, Pennside Partners, Pfizer, Regeneron, Sanofi-Genzyme, Sun Pharma. **Mark D. P. Davis, MD:** none. **Nicole Fett, MD:** Hoffman La Roche, Pfizer. **Sheilagh M. Maguiness, MD:** Regeneron Pharmaceuticals. **Kishwer S. Nehal, MD:** none. **Vikash S. Oza, MD:** Pfizer, Regeneron Pharmaceuticals. **Misha A. Rosenbach, MD:** Derm101.com, JAMA Dermatology, Merck, Processa Pharma, Up To Date Online. **Janet Schlechte, MD:** none.

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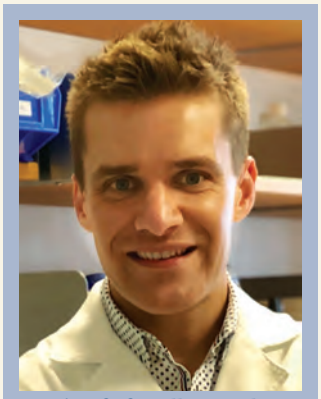
Stiefel Scholar Awardee's Revolutionary Treatment Goal—Reversing Keratinocyte Carcinomas

Brian C. Capell, MD, PhD—Assistant Professor of Dermatology and Genetics at the University of Pennsylvania—is the second recipient of the DF's midcareer Stiefel Scholar Award in Skin Cancer. This support is enabling him to make critical progress in the groundbreaking treatment he is working toward for keratinocyte carcinomas (KCs). Instead of attacking the malignant cells, his treatment will transform them into healthy tissue—and keep them that way.

Dr. Capell's innovative progress involves *epigenetics*, "the system of regulatory enzymes that basically determines which genes get turned on or off in every cell in our body," he explains. "DNA is the blueprint of life," he continues. "Every cell in our body has the identical blueprint. These regulatory enzymes essentially create the 200 different cell types in our body by determining the genes that are turned on or off in each cell type." Dr. Capell has focused on the chromatin-regulating family of enzymes in the skin because their cutaneous roles were unknown, and they are frequently dysregulated in KCs. These skin cancers—basal cell carcinomas (BCC) and cutaneous squamous cell carcinomas (cSCC)—are a major public health burden. The combined number of patients diagnosed annually far exceeds the sum of all other cancers. Surgical treatment risks disfigurement, and mortality is a significant risk among elderly and immunocompromised patients.



Brian C. Capell, MD, PhD

Dr. Capell discovered that a chromatin regulator (LSD1) turns off the keratinocyte's differentiation genes and is frequently overexpressed in KCs. Then he observed that after he added LSD1 inhibitors to cSCC cultures, the malignant cells turned on those tumor-suppressive differentiation genes and behaved like normal keratinocytes. Now Dr. Capell's lab is dissecting out all of the chromatin-regulating enzymes relevant for KCs and preparing to carry out further testing, both on LSD1 inhibitors and on other novel targeted epigenetic therapies aiming to normalize the cancer cells.

Early career DF funding enabled Dr. Capell to begin his insightful epigenetics research in the skin. Now his Stiefel Award in Skin Cancer is supporting crucial progress in understanding skin biology and pioneering a new approach to treating KCs. "I cannot say enough about the critical support this award provides. Without it, we wouldn't be able to ask the questions we are asking right now," Dr. Capell says. Ultimately, he hopes to harness the powerful potential of epigenetic therapies for skin disease in general.

The Foundation is deeply grateful to Charles and Daneen Stiefel for their generous gift of $1 million to fund three midcareer awards for outstanding investigators driving progress in understanding and treating skin cancers.

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VOL. 38 NO. 2 FALL 2019