The University of North Carolina at Chapel Hill School of Medicine
Department of Dermatology
Presents

The 36th Annual
Southeastern Consortium For CME in Dermatology

Immunological Diseases, Therapeutic Dilemmas, and What's New in 2012

Friday-Sunday, October 26-28, 2012

The William and Ida Friday Center
for Continuing Education
100 Friday Center Drive
Chapel Hill, North Carolina 27517

in Partnership with Greensboro AHEC

University of North Carolina at Chapel Hill School of Medicine

Department of Dermatology

Gratefully acknowledges the financial support of the following exhibitors:

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General Information

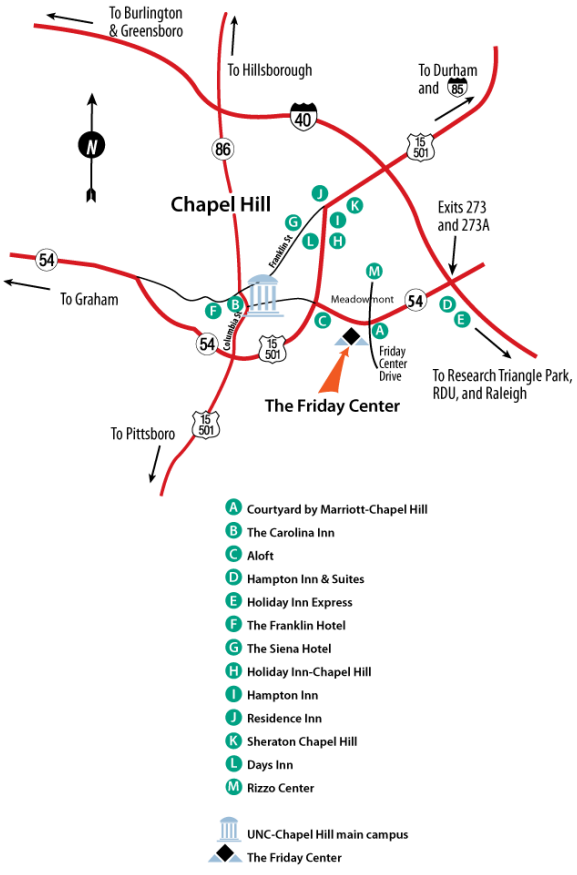
Friday and Saturday's sessions will take place at The William and Ida Friday Center for Continuing Education (The Friday Center), in the Grumman Auditorium.

Out of respect to our speakers and other attendees, please set pagers/phones on vibrate during the didactic sessions. Please wear badges to all sessions and session breaks. Posters and exhibits are open for viewing from 11:30 am Friday through 12:45 pm Saturday.

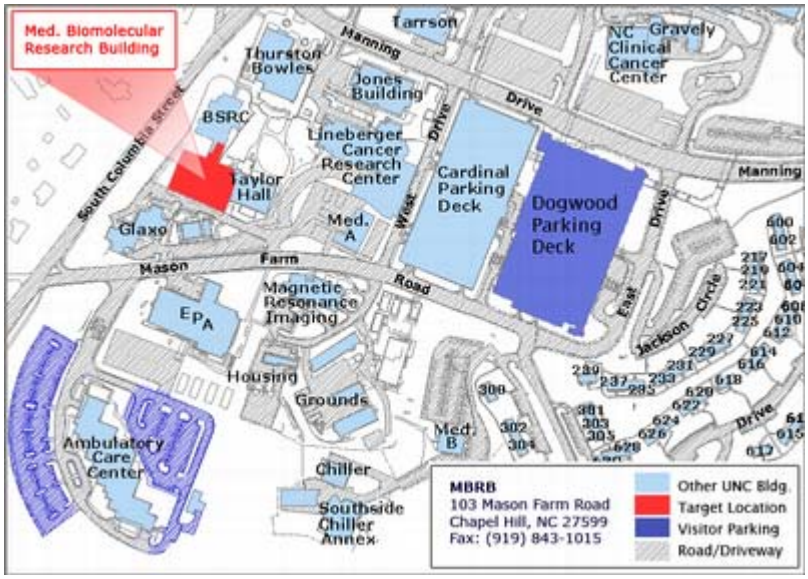
On Friday evening from 5:30-7:30 pm, please join faculty and other attendees at the reception, which will be held in the Atrium, just outside the Grumman Auditorium.

The Sunday morning session will be held on the UNC Campus from 7:45 am to 12:00 pm. Patient viewing will take place at the Ambulatory Care Center (ACC) at 100 Mason Farm Road from 8:30-10:00 am, preceded by breakfast/registration at 7:45 am. The patient discussion will take place in G202 Medical Biomolecular Research Building (MBRB) from 10:15 am – 12:00 pm. Signs will be posted.

Shuttle bus service to and from the Courtyard Marriott to the ACC will be available. Buses will depart at 7:20 am Sunday morning from the Courtyard Marriott. Return bus service is scheduled to depart from the ACC at 12:20 pm.



Complimentary parking is available at The Friday Center for the didactic sessions on Friday and Saturday, and complimentary parking is available on Sunday at the Ambulatory Care Center (ACC). Park on the left side of the ACC, to enter the building on the second floor. (in the below map, parking is the shaded area to the right of the ACC). The MBRB Building is a short walk across Mason Farm Road.



On Sunday, a continental breakfast will be provided.

CME certificates will be available once the online evaluations are submitted. Instructions on how to access the online evaluations and online certificates will be distributed at the conference.

Please check with the hotel staff regarding check out times on Sunday, as it may be necessary to check out prior to departure for the Sunday patient session.

Save the date!

SEC 2013
Hosted by
University of Alabama at Birmingham

Program Description

This symposium is designed for dermatologists in private practice or academia, dermatology residents and fellows, and mid-level providers in dermatology. The program includes half day didactic sessions on Friday afternoon and Saturday morning, and patient viewing followed by the patient case discussion on Sunday.

The purpose of the annual SEC meeting is to support the educational collaboration of dermatologists in the Southeastern United States. Each year, the meeting rotates among the 10 participating university dermatology programs. This year's meeting will highlight immunological diseases, therapeutic dilemmas, and what's new in 2012.

At the conclusion of this program, the participant should be able to:

- Identify treatment options for high-risk skin tumors.
- Use a proposed algorithm for treating hand eczema.
- Identify new treatment strategies for cutaneous diseases.
- Learn the new uses of rituximab in autoimmune blistering diseases.
- Learn new strategies in the management of itch.
- Update knowledge of hyperhidrosis.
- Be better equipped to diagnose rare and complicated diseases.
- Update knowledge in the bullous immunological diseases.
- Enhance knowledge in relevant historical data, milestones in immunological research, diagnostic procedures, and therapy of these patients.
- Identify emerging and newly described clinicopathologic entities.

Continuing Education Credit

Greensboro AHEC designates this live activity for a maximum of 11.5 AMA PRA Category I credit(s).™ Physicians should claim only the credit commensurate with the extent of their participation in this activity.

This activity has been planned and implemented in accordance with the Essentials and Standards of the North Carolina Medical Society. Greensboro AHEC is accredited by the NCMS to provide continuing medical education for physicians. Greensboro AHEC adheres to the ACCME Standards regarding industry support of continuing education.

Disclosure Statement

Greensboro AHEC adheres to the ACCME Standards regarding industry support of continuing education. Disclosure of the planning committee and faculty's commercial relationships, if any, will be made known at the time of the activity. Speakers will also state when off-label or experimental use of drugs or devices is incorporated in their presentation. A list of supporters, if any, will be made at the time of the activity.

The 36th Annual Southeastern Consortium for CME in Dermatology

Program Chair

Aída Lugo-Somolinos, MD
Professor, Dermatology

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Assistant Professor, Dermatology

Guest Faculty

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Professor & Chair, Dermatology
University of Virginia

Alma Cruz, MD
Assistant Professor, Dermatology
University of Puerto Rico

Russell Hall, MD
J. Lamar Callaway Professor & Chair, Dermatology

Duke University
HERBERT Z. LUND LECTURE:
John Stanley, MD
Professor, Dermatology
University of Pennsylvania

Robert Swerlick, MD
Alicia Leizman Stonecipher Professor & Chair, Dermatology
Emory University

Gil Yosipovitch, MD
Professor, Dermatology
Wake Forest University

The University of North Carolina at Chapel Hill School of Medicine Faculty

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Assistant Professor, Dermatology

CLAYTON E. WHEELER LECTURE:
Luis Diaz, MD
C.E. Wheeler, Jr. Distinguished Professor & Chair, Dermatology

Puneet Jolly, MD, PhD
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Aída Lugo-Somolinos, MD
Professor, Dermatology

Brad Merritt, MD
Assistant Professor, Dermatology

Dan Zedek, MD
Assistant Professor, Dermatology

PROGRAM AGENDA

Friday, October 26

11:30 am	Registration/Exhibits/Posters open – in the Atrium
12:55 pm	Welcome/Opening Remarks *Aída Lugo-Somolinos, MD*

Immunological Diseases

Moderator:	*David Rubenstein, MD, PhD*
1:00 pm	The Use of Rituximab in Autoimmune Blistering Disorders *Donna Culton, MD, PhD*
1:40 pm	Management of Pruritus in Inflammatory Skin Diseases *Robert Swerlick, MD*
2:20 pm	Pathogenesis of Dermatitis Herpetiformis: A Model for Gut-Associated Skin Diseases *Russell Hall, MD*
3:00 pm	Break/Exhibits/Posters
3:30 pm	Pathophysiology and Therapeutic Implications from Cloning Pemphigus Antibodies *John Stanley, MD*
4:10 pm	**Clayton E. Wheeler Lecture** Milestones in Pemphigus and Pemphigoid Pathogenesis *Luis Diaz, MD*
5:10 pm	North Carolina Dermatology Association Meeting
5:30 pm	Reception – Atrium

Saturday, October 27

7:30 am	Continental Breakfast/Exhibits/Posters
7:55 am	Welcome/Opening Remarks *Aída Lugo-Somolinos, MD*

Therapeutic Dilemmas

Moderator:	*Nancy Thomas, MD, PhD*
8:00 am	Primary Focal Hyperhidrosis *Alma Cruz, MD*
8:30 am	Urticaria, Angioedema, and Delayed Pressure Urticaria *Thomas Cropley, MD*
9:00 am	My Approach to Hand Eczema *Aída Lugo-Somolinos, MD*
9:30 am	**Herbert Z. Lund Lecture** Lessons from Pemphigus Research on How to be a Physician Scientist *John Stanley, MD*
10:30 am	Break/Exhibits/Posters

What's New

Moderator:	*Amy Fox, MD*
11:00 am	Itching: What's New *Gil Yosipovitch, MD*
11:30 am	What's New in Dermatopathology *Dan Zedek, MD*
12:00 pm	Surgical and Medical Management of High-Risk Skin Tumors *Puneet Jolly, MD, PhD* and *Brad Merritt, MD*
12:45 pm	Presentation of Poster Awards *Dan Zedek, MD* and *Puneet Jolly, MD, PhD*

Sunday, October 28

Patient Presentations

Ambulatory Care Center (ACC)
UNC Campus
100 Mason Farm Road
Chapel Hill, NC 27599

7:20 am	Shuttle departs Courtyard Marriott
7:45 am	Registration/Continental Breakfast – 2nd floor lobby
8:30 am	Patient Viewing – 3rd floor

Clinical Session

Medical Biomolecular Research Building (MBRB)
UNC Campus
103 Mason Farm Road
Chapel Hill, NC 27599

Moderators:
Craig Burkhart, MD
Dean Morrell, MD

10:15 am	Case Discussions – Room G202
12:00 pm	Adjournment
12:20 pm	Shuttle departs for Courtyard Marriott (from the ACC Building)

The Use of Rituximab in Autoimmune Blistering Disorders

Donna Culton, MD, PhD

The use of rituximab in autoimmune blistering disorders

Donna Culton, MD, PhD
University of North Carolina, Chapel Hill, North Carolina
36th Annual Southeastern Consortium in Dermatology
October 26, 2012

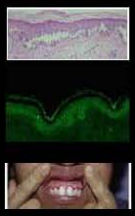
UNC

Overview

- Autoimmune blistering disorders pathophysiology review
- Rituximab – questions….
  - How does it work?
  - When should we use it?
  - How should it be given?
  - Is it safe?

Pemphigus vulgaris

- Histologic features
  - Suprabasilar cleft with acantholysis
- Immunofluorescence
  - Intercellular space (ICS) staining with IgG
- Clinical features
  - Flaccid bullae and erosions of the mucosa and skin



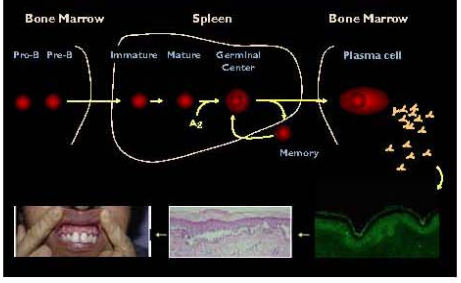
Ramos-e-Silva M, et al. Clin Dermatol 2011;29:443-54.

Treatment of pemphigus

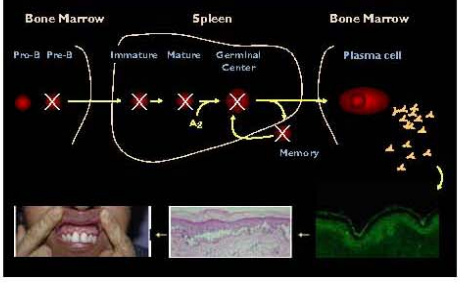
- Historically, mortality in pemphigus was 50% at 1 year when left untreated
- Introduction of systemic corticosteroids in 1950s
- Addition of systemic immunosuppressives as steroid sparing agents in 1960s
  - Azathioprine, mycophenolate, cyclophosphamide
- Therapies aimed at eliminating circulating autoantibodies
  - Plasmapheresis, intravenous immunoglobulin (IVIg)
- Rituximab – a way to specifically target B lymphocytes

Culton DA et al. J Autoimmun 2008;31:311-24.

B lymphocytes in pemphigus



B lymphocytes in pemphigus



Rituximab

- How does it work?
  - Mechanism of action
  - B cell changes
  - T cell changes
  - Antibody changes

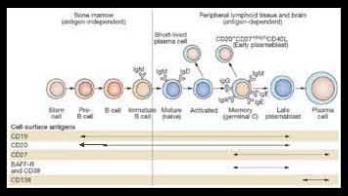
Rituximab and CD20

- Chimeric murine/human monoclonal antibody that recognizes the B lymphocyte surface protein CD20
- CD20 is a transmembrane protein expressed on pre-B to mature B cells and functions to regulate B cells early in development
- CD20 is an ideal B cell target
  - Not shed from the cell surface
  - Not found in circulation
  - Does not internalize upon binding
  - Not expressed on other tissues/cells

Pescovitz MD. Am J Transplant 2006;6:859-66.

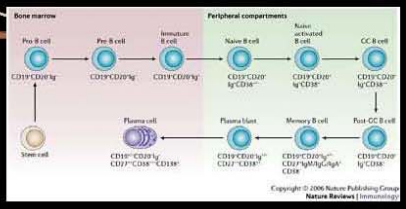
Rituximab and CD20

- CD20 is not expressed on pro-B cells or plasma cells



Dalakas MC. Nat Clin Pract Neurol 2008;4:557-567.

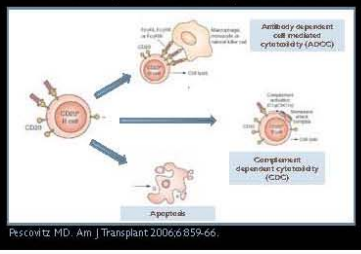
Rituximab and CD20



Edwards JCW, et al. Nat Rev Immunol. 2006;6:394-403.

Mechanism of action

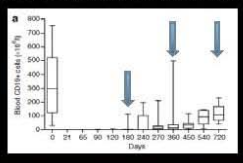
- Rituximab binding to CD20 results in rapid elimination of B cells



Pescovitz MD. Am J Transplant 2006;6:859-66.

B cell changes following rituximab

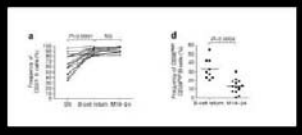
- After a single infusion of 100 mg/m^2, peripheral blood B lymphocytes are nearly completely eliminated
- B cell repletion begins at approximately 6 months



Edwards JC and Cambridge G. Nat Rev Immunol 2006;6:394-403.
Mouquet H et al. J Invest Dermatol 2008;128:2859-69.

B cell changes following rituximab

- Studies in pemphigus (and rheumatoid arthritis) have shown that repopulation is dominated by naïve and immature B cells



Leandro MJ, et al. Arthritis Rheum 2006;54:613-20.
Mouquet H et al. J Invest Dermatol 2008;128:2859-69.

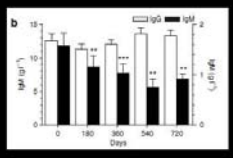
T cell changes following rituximab

- Studies in pemphigus have shown that rituximab induces a significant reduction of Dsg3 specific CD4+ Th1 and Th2 cells
- Overall CD3+ and CD4+ counts and tetanus toxoid reactive CD4 Th cells are unaffected
- Possibly due to the depletion of autoreactive B cells, which can serve as antigen presenting cells and provide necessary costimulatory signals for T cell activation

Ming R, et al. J Invest Dermatol. 2008;128:2850-8.

Antibody changes following rituximab

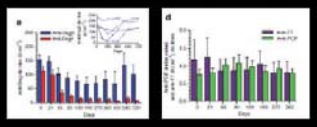
- Total serum IgG has not been shown to decrease significantly, while total serum IgM falls



Mouquet H et al. J Invest Dermatol. 2008;128:2859-69.

Antibody changes following rituximab

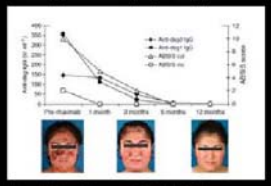
- Specific decrease in anti-Dsg antibodies (Dsg1>Dsg3)
- Levels of IgG to HSV, tetanus toxoid, and pneumococcal capsule were stable (or increased) following rituximab



Mouquet H et al. J Invest Dermatol. 2008;128:2859-69.
Nagel A, et al. J Invest Dermatol. 2009;129:2202-10.
Ming R, et al. J Invest Dermatol. 2008;128:2850-8.

Antibody changes following rituximab

- Clinical response tends to correlate with a decrease in anti-Dsg antibodies (Dsg1>Dsg3)



Ming R, et al. J Invest Dermatol. 2008;128:2850-8.

Rituximab

- When should we use it?
  - Common uses
  - Indications
  - Contraindications
  - Predictors of response

Common uses

- Initially used to treat B cell malignancies
- Use expanded to antibody mediated autoimmune diseases
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Autoimmune hemolytic anemia
  - Idiopathic thrombocytopenic purpura
  - Autoimmune blistering disorders

Indications for rituximab in pemphigus

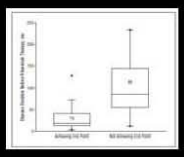
- Documented cases of pemphigus vulgaris or pemphigus foliaceus by clinical, histologic, and immunofluorescence findings
- Involvement of at least 30% of body surface area and/or three or more mucosal surfaces
- Lack of response or multiple relapses despite high dose prednisone, immunosuppressive agents, and/or IVIg OR contraindications/side effects to corticosteroids and immunosuppressive agents

Potential use earlier in disease

Adjuvant Rituximab Therapy of Pemphigus

A Single-Center Experience With 31 Patients

- 31 patients failing standard therapy
- Endpoint - Complete remission taking no or minimal therapy
  - 18/31 (58%) achieved the endpoint
  - Those achieving the endpoint had a lower median disease duration



Lunardon L, et al. Arch Dermatol. 2012;148:1031-1036.

Contraindications for rituximab

- Pregnancy or breastfeeding
- <18 years of age
- Known allergy to murine proteins
- Active hepatitis B, hepatitis C, or tuberculosis
- HIV infection (CD4 count <250 cells/ul)
- Severe heart failure (NYHA II-IV)
- Uncontrolled infection

Predictors of response

- Percentage of plasmablasts in the peripheral blood
- Level of BAFF surge post rituximab
- IL6 polymorphisms
- Human antichimeric antibodies
- FcγRIIIa polymorphisms (lymphoma)

Lunardon L, et al. J Allergy Clin Immunol. 2012;130:800-3.
Giachelia M, et al. Leuk Lymphoma. 2012;53:411-6.
Brezinschek HP, et al. Arthritis Res Ther. 2012;14:R161.
Edhegard K, et al. JID. 2011;131:S10.

Rituximab

- How should it be given?
  - Dosing schedules
  - Pre-treatment labs
  - Post-treatment monitoring

Rituximab dosing schedules

- Two common dosing protocols
  - Lymphoma protocol
    - 375 mg/m^2 IV once weekly for 4 consecutive weeks
  - Rheumatoid arthritis protocol
    - 1000mg IV administered at day 0 and day 15
- Multiple off-label protocols have been used
- Often combined with other systemic therapy, such as corticosteroids or immunosuppressives

Rituximab dosing schedules

SLE

- No difference in clinical remission or B cell depletion with a single IV infusion of 100mg/m^2 compared to 375mg/m^2 given either once or as 4 weekly infusions

RA

- No additional benefit when administering 375mg/m^2 in two versus four weekly infusions

Anolik JH, et al. Arthritis Rheum. 2004;50:3580-90.
Leandro MJ, et al. Ann Rheum Dis. 2002;61:883-8.

Rituximab dosing schedules in PV

Joly P, et al. NEJM. 2007

- 21 patients
- 375mg/m^2 was administered as 4 weekly infusions
- Complete remission in 86% of patients at 3 months, sustained for 34 months
- Time to complete remission
  - Median 3 months
- Relapse rate
  - 42% relapse (median 18 months)

Joly P et al., NEJM. 2007;357:545-52.

Rituximab dosing schedules in PV

Cianchini G, et al. JAAD. 2012

- 42 patients
- 1000 mg administered at day 0 and day 15
- Complete remission in 86% at 6 months
- Time to complete remission
  - Median 70 days (about 2 months)
- Relapse rate
  - 48% relapse (median 16 months)

Cianchini G, et al., JAAD. 2012;67:617-22.

Rituximab dosing schedules in PV

Kim JH, et al. Br J Dermatol. 2011

- 27 patients
- 375mg/m^2 was administered as 2 (n=12) versus 3 or more (n=15) weekly infusions
- Complete remission in 75% of the high dose group and 42% of the low dose group
- Improved time to complete remission with high dose
  - Median 149 days versus 433 days (p=0.06)
- Decreased relapse rate with high dose
  - 0% relapse (median 18 month follow up) versus 67% relapse (11 month follow up) (p<0.01)

Kim JH, et al. Br J Dermatol. 2011;165646-651.

Rituximab dosing schedules in PV

Horvath B, et al. Br J Dermatol. 2012

- 15 patients
- 500mg administered at day 0 and day 15
- Complete remission in 53% (versus 86% in patients receiving the standard R.A protocol)
- Longer time to complete and partial remission
  - PR – Median 34.5 weeks (versus 13 weeks)
  - CR – Median 51 weeks (versus 26 weeks)
- Similar relapse rate
  - 40% relapse – Median 97 weeks follow up (versus 48%)

Horvath B, et al. Br J Dermatol. 2012;166:405-412.

Labs and monitoring

- Before initiating therapy:
  - CBC with differential and absolute B cell count
  - UPT, hepatitis, HIV serologies and PPD
  - Anti-Dsg titers
- After therapy (1 month after and then every 3 months):
  - CBC with differential and absolute B cell count
  - Anti-Dsg titers

Pre-treatment vaccinations

- Vaccinations should be administered 1 month before or 6 months after treatment
  - Risk of ineffective antibody response in protein based or inactivated vaccines
  - Risk of increased infectivity in live vaccines
- Consider administering influenza, tetanus, pneumococcal, and herpes zoster vaccines at least one month prior to treatment

Giving the infusion

- Most dermatologists partner with an infusion center
- The coadministration of systemic corticosteroids and diphenhydramine reduces infusion related adverse effects
- The first infusion is typically given over 5 hours with subsequent infusions given over 3-5 hours if well tolerated

Rituximab

- Is it safe?

Safety

Infusion reactions

- Mild – Fever, chills, headache, pruritus, urticaria
- Severe – Angioedema, bronchospasm, hypotension

Tony et al. Arthritis Research & Therapy 2011, 13:R75.

Safety

Non-infusion related severe side effects
(5-11% of patients)

- Infection, severe
  - 7% of pemphigus patients on rituximab
  - 1st 6 months critical period
- Deep vein thrombosis
- Neutropenia
- Progressive multifocal leukoencephalopathy
  - Not yet reported in AIBD patients

Tony et al. Arthritis Research & Therapy 2011, 13:R75.
Feldman RJ and Ahmed AR. Expert Rev Clin Immunol. 2011;7:529-41.

Safety

Table 1. Adverse events observed in pemphigus vulgaris patients treated with rituximab.

Adverse event	Rituximab with prednisone + IVA	Rituximab with prednisone	Rituximab alone
Total adverse events (n = 17)	14 (82%)	2 (12%)	1 (6%)
Hypogammaglobulinemia	2		1
DVT	1		
PE	2		
Infections (n = 11)			
Pneumonia	5		
CMV gastroenteritis	1		
Septic arthritis	1		
Pyelonephritis		1	
Sepsis	2	1	

Specific adverse events are listed in patients receiving concomitant therapy with prednisone plus IVA versus prednisone alone versus rituximab monotherapy.
CMV, Cytomegalovirus; DVT, Deep venous thrombosis; IVA, Immunosuppressive agent; PE, Pulmonary embolus.

Feldman RJ and Ahmed AR. Expert Rev Clin Immunol. 2011;7:529-41.

What about AIBD other than pemphigus?

Mucous membrane pemphigoid

- 25 patients
- 375mg/m^2 was administered as 4 weekly infusions
- Complete remission 88% after 1 or 2 cycles
- Relapse – 45% after a mean of 4 months

Le Roux-Villet C, et al. Arch Dermatol. 2011;147:843-9.

What about AIBD other than pemphigus?

Bullous pemphigoid

- 7 patients
- 1000mg administered on day 0 and day 15
- At 12 months 5/7 patients were off prednisone
- 2 patients experienced a flare, correlating to lower BAFF surge post rituximab and preferential recovery of IgD- memory cells after B cell repopulation

Edhegard K, et al. JID. 2011;131:S10.

Questions remain

- Does rituximab have other mechanisms aside from eliminating B lymphocytes?
- Expanding clinical uses – refractory pemphigoid
- Use of rituximab in early or mild disease
- Predictors of response, relapse
- Long term safety profile

Management of Pruritus in Inflammatory Skin Diseases

Robert Swerlick, MD

Management of Pruritus in Inflammatory skin diseases

Robert A. Swerlick, MD
Alicia Leizman Stonecipher Chair of Dermatology
Professor and Chairman, Department of Dermatology
Emory University School of Medicine

COI and Disclaimer

- I have no financial COI relevant to this presentation
- I will extensively discuss off label use of drugs
- This is a biased talk whose conclusions are supported by limited hard data
  - Biased sample
  - Personal experience

Talk outline and goals

- Review my experience with patients who present to a referral center with pruritic inflammatory skin disorders
- Highlight new data collection tools and their potential to impact how we practice
- Describe my diagnostic and therapeutic approaches and well as decision making strategies
- Highlight new management tools centered on the use of thiopurine agents

Who is itchy and how bad is their problem?

- No great population based data
- My conclusions are drawn from my practice
  - Referral bias – what ends up at the end of the funnel that leads to me may not be representative
  - My conclusions are based upon a VERY biased sample
  - However, it is all I have to work with!

My biased assumptions

- Itching is the major source of morbidity associated with skin diseases
- The overwhelming majority of pruritic patients have itch as a consequence of inflammatory skin diseases
- Itch tends to be ignored and undertreated since physicians tend to focus on objective findings as opposed to subjective issues

tch and Inflammatory Skin disease: Review of the literature

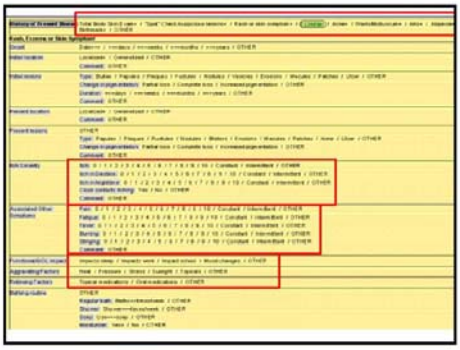
- Atopic Dermatitis – almost universal itch; 10-15% of children; 2.5% disease prevalence overall
- Psoriasis – > 85% of patient report itch, perhaps more moderate that AD. Patients relate itch as more impactful than arthritis or pain
- Urticaria – up to 20% of population affected in lifetime – all itch to varying degrees
- Urticarial dermatitis – distinct from common hives
- Other – bullous diseases, LP, ACD, xerosis…

Key questions for which we have limited answers

- How common is itch?
- Which of our patients itch?
- How badly do they itch?
- When do they itch?
- How does itch affect their lives?
- What therapy makes them better?
- What therapy creates new problems?

Assessment tools

- We are trying to move to a data driven environment
- Need data collection tools embedded in our regular work flow which allow for the capture of structured data – "Data holy grail"
- EHR – both blessing and curse
  - We have built structured templates into our EHR to allow us to answer fundamental questions about itch, frequency, impact, and response to treatment



Itch assessment tools

- Visual analogue scales
- QOL instruments – ItchQol
- Eppendorf itch questionnaire
- 5-D itch scale
- Itch scores embedded in other measures
  - SCORAD

Assessment tools

- How we measure success?
  - I rely on patient and MD defined end-points
  - For itch, if the patient defines therapy as being adequate for the itch they are experiencing, who am I to argue?

Assessment tools

- We are deploying tablets and having patients enter data into a REDCap database
  - ItchyQol
  - DLQI
- We are hopeful that this will allow us to better define who we are seeing, for which diseases, how their pruritic disease impacts them, and what really works in terms of treatment
- Next time I present, more hard data

What pruritic skin diseases present in my practice

- Overwhelmingly what presents in referrals to me appears to be a mixture of inflammatory skin diseases associated with itching
- Labels/Dx used by referring MDs
  - Eczema/dermatitis
  - Drug eruption
  - Contact dermatitis
  - Urticaria
  - Bullous diseases

What I end up diagnosing

- Definable triggers – only a minority of patients
  - Scabies
  - Contact dermatitis
  - Systemic contact dermatitis/ingestant driven dermatitis
  - Blistering diseases
  - Rarely other causes identified – renal, hepatic, hematological, neurological, metabolic driven itch
- No definable triggers – vast majority of what I see
  - Eczema/psoriasiform dermatitis (?psoriasis)
  - Urticaria
  - Urticarial dermatitis

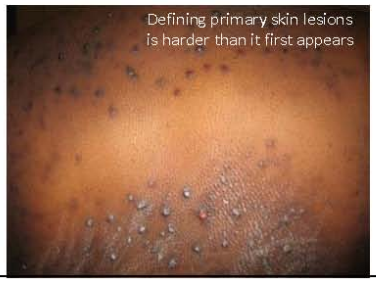
How I approach the "itchy" patient

- Look for a "fixable" etiology for the pruritic disorder - I have no magic formula
  - Diagnostic tests – limited utility (similar to CIU workup)
    - KOH – occult scabies or dermatophyte
    - Skin biopsy – low yield – R/O CTCL –rarely changes treatment
    - Patch testing – yield depends on pre-test prob.
    - Basic labs – rarely illuminating
    - Stool cultures, H. pylori serology/stool test
  - Be persistent – even if you don't find anything patients expect you to keep trying

Ingestant Triggers

- Needle in a haystack problem
- Ingestants may trigger itch via an urticarial but not IgE dependent mechanism
  - ImmunoCap or RAST testing may not be useful
  - Reactions may be immediate or delayed
- Foods, drugs, additives/excipients
  - Balsam of Peru/fragrance
  - Food and medication dyes
  - Elimination diets are difficult and often unhelpful

Rash that itches vs. itch that rashes



Empiric treatment

- When you cannot find a cause for the itch, which is very common, you are left with empiric treatment
- Parallel approaches – keep looking and keep treating
- Which approaches to take?
  - Topical vs. systemic agents
  - Anti-pruritics vs. anti-inflammatory agents

Therapeutic ladder I

- Emollients and TCS – useful for eczematous and 1° papulosquamous disease
  - Hydration followed by topical agents ("Soak and grease" per Dr. Ken Greer)
  - Treat infected eczema component – systemic antibiotics vs. topicals vs. bleach baths
  - TCI's of very limited benefit in my experience
  - Check Vitamin D status, especially in dark skinned patients
- Urticaria and urticarial dermatitis – intensive topicals may objectively clear the skin but have little or no lasting effect on itch
  - Ask about the intensity of the itch!

Urticarial Dermatitis

- Aka – Dermal hypersensitivity reaction
  - Kossard et al, Arch Dermatol Jan 2006 and Fung, JAAD 2002
  - Clinical and histological overlap with urticaria, spongiotic dermatitis, occult pemphigoid, drug reaction, and urticarial vasculitis.
  - Superficial and deep perivascular infiltrates with eosinophils
  - Very persistent disease – large segment of patients referred to me – no definable/removable triggers

Therapeutic ladder I

- Urticaria and urticarial dermatitis – push antihistamines and anti-leukotrienes. Non-sedating agents may be useful
  - Non-sedating agents for daytime use – may push dose beyond package insert (fexofenodine, cetirizine)
  - Sedating agents for night time – doxepin (liquid formulation) – allows for titration to tolerance
  - I find zafirlukast more effective than montelukast
- Eczematous reactions and non-urticarial pruritic skin diseases – benefit of antihistamines not so clear unless they are very sedating

Therapeutic ladder II

- What if they don't respond adequately with first line Rx?
  - Systemic Corticosteroids
  - Other anti-pruritics – SSRI's, gabapentin, opiate antagonists, thalidomide
  - UVL
  - Steroid sparing agents - Azathioprine, Methotrexate, Mycophenylate, Cyclosporine or Tacrolimus

Systemic corticosteroids

- Very effective in my hands for the overwhelming majority of patients who present with itch – what does this mean?
  - Can use as a "litmus test" – I infer an inflammatory etiology in those who have an unambiguous response
  - I also infer likely response to steroid sparing, anti-inflammatory agents
  - Follow the Iraq and Afghanistan principle – always need an exit strategy

Systemic corticosteroids

- Chronic use may be limited by long term sequel
  - Bone issues, mood alterations, weight gain, hypertension, glucose intolerance
- Trade offs between safety and effectiveness
  - Route of delivery, divided vs. single daily dose, lack of rigorous longitudinal data on side effects
- Bias – those referred to me generally have suffered some sort of corticosteroid sequel

Other oral anti-pruritics

- Gabapentin, opiate antagonists (naloxone)
  - limited benefits in my hands – may be due to referral bias
- Thalidomide - specific logistical challenges
  - STEPS makes iPledge appear easy.

Ultraviolet Light

- Limited personal experience with UVL for the treatment of itching at Emory based upon three factors
  - Time commitment in my patients precludes widespread use except in patients who have lots of time on their hands
  - Copayment costs fall heavily upon many patients in our system - $30 copay for each treatment
  - Personal bias – of all the modalities deployed, UVL is the only known carcinogen

UVL Time constraints

- Assumptions at Emory Clinic and Atlanta VA
  - Three times weekly treatment
  - Travel time and office time
    - To TEC or VA 60 minutes, inclusive or parking and getting to the clinic. For those who live > 10 miles from us, this estimate is too conservative. Parking at the VA may take more than one hour.
    - Office time induding check in, rooming, undressing and dressing, light treatment, and check out – 30 minutes
  - Weekly time commitment at least 5 hours and may be greater than 10 hours
- What is the value of patient time? Which of you could devote this amount of time?

Therapeutic ladder III

- How do I decide when to get more aggressive?
  - How impactful is the itch?
  - What is <u>your</u> risk tolerance and what is your patient's risk tolerance?
  - Medical decision vs. personal decision – is aggressive treatment warranted?
    - Both patient and provider have veto power
- Which agent is preferable and why?
  - Risk tolerance of patient and of physician

How can one decide whether the risks of treatment are warranted?

- What is the likelihood of success?
  - How is success defined?
  - Objective vs. subjective measures
  - Pt vs. doctor perceived
- How do we and patients decide in general?
  - Gut vs. Head
- What are the risks and how can we communicate them?
  - Are we dealing with data or anecdote?
  - How do we frame the questions?

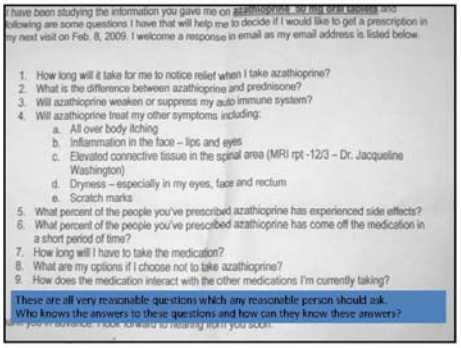
Now imagine your doctor discovered that you suffered from 'SPF 2'. Please tick the answer that is closest to how you would react:

1. Would you take the pills described above if they reduced your risk of having a stroke by 45%? *(risk reduction model)*
2. What if you were unlikely to have a stroke, so that it worked out that in a year you would have only a 1 in 400 chance of having a stroke, but the pills could reduce this to a 1 in 700 chance? Would you take the pills? *(absolute risk reduction model)*
3. If the doctor had to treat 35 patients for 25 years in order to prevent one stroke, do you think it would be worth taking the treatment for yourself? *(number needed to treat model)*
4. If the tablets had a 3% chance of doing you good by preventing a stroke and a 97% chance of doing no good or not being needed in your case would you take them? *(personal probability of benefit from treatment model)*

Table 1. Risk and treatment.

Would you take treatment?	Relative risk reduction (%)	Absolute risk reduction (%)	Number needed to treat (%)	Personal probability of benefit (%)
Definitely	180 (65)	129 (47)	96 (35)	50 (18)
Maybe	75 (27)	79 (29)	92 (33)	71 (26)
Probably not	14 (5)	46 (17)	63 (23)	91 (33)
Definitely not	7 (3)	22 (8)	25 (9)	64 (23)
Proportion accepting treatment (95% CI)	92% (89-96%)	75% (70-80%)	68% (63-74%)	44% (38-50%)

D Misselbrook and D Armstrong. 276. British Journal of General Practice, April 2001



I have been studying the information you gave me on azathioprine. So that I can [illegible] and following are some questions I have that will help me to decide if I would like to get a prescription in my next visit on Feb. 8, 2009. I welcome a response in email as my email address is listed below.

1. How long will it take for me to notice relief when I take azathioprine?
2. What is the difference between azathioprine and prednisone?
3. Will azathioprine weaken or suppress my auto immune system?
4. Will azathioprine treat my other symptoms including:
   a. All over body itching
   b. Inflammation in the face – lips and eyes
   c. Elevated connective tissue in the spinal area (MRI rpt -12/3 – Dr. Jacqueline Washington)
   d. Dryness – especially in my eyes, face and rectum
   e. Scratch marks
5. What percent of the people you've prescribed azathioprine has experienced side effects?
6. What percent of the people you've prescribed azathioprine has come off the medication in a short period of time?
7. How long will I have to take the medication?
8. What are my options if I choose not to take azathioprine?
9. How does the medication interact with the other medications I'm currently taking?

These are all very reasonable questions which any reasonable person should ask. Who knows the answers to these questions and how can they know these answers?

[illegible] you in advance. I look forward to hearing from you soon.

Risk of Immunosuppressive Drugs

- Risk of infection
  - Which ones?
  - How large is the risk?
- Risk of malignancy
  - Which ones?
  - How large is the risk?
- Risk compared to daily oral corticosteroids?
- What are the risks associated with the underlying disease?

Immunosuppressive agent risks: Data sources and limits

- Transplant literature
  - Strengths include large numbers followed for extended times, many of the drugs we use
  - Weaknesses include use of multiple IS agents simultaneously, extended length of treatment, treatment initiated immediately after surgical event
- TNF inhibitor registries
  - Strengths include relatively large numbers of patients with comparisons to DMARDs (mostly MTX)
  - Weaknesses - include limited data on agents widely used in dermatology
- Other large studies

What do we know about the risks of immunosuppressive agents?

- The data regarding the agents we presently use are incomplete
  - The risk is low enough to require large patient populations to define the size of the risk
    - Magnitude of risks comparable to NSAID trials where almost 150K people were enrolled in RCT and 3.5 million were followed in observational studies (http://arthritis-research.com/content/10/1/R20)
  - We can estimate the order of magnitude of risk we are dealing with

What do we know about the risks of immunosuppressive agents?

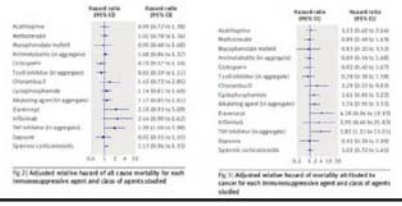
- Infections – TB data and comparisons to DMARDs (MTX)- most RA patients
  - Risk of reactivation around 1-2:1000 in unscreened populations with relatively high incidence of PPD positive individuals
    - Higher risk with anti-TNF mab
    - Likely influenced by underlying conditions (RA/SLE)
    - Studied in populations where there are higher rates of latent TB
  - Other infections – data confusing since patients with worse disease require more intensive treatment
  - Response to immunization – blunted with AZA and MTX but not so much with biologic agents

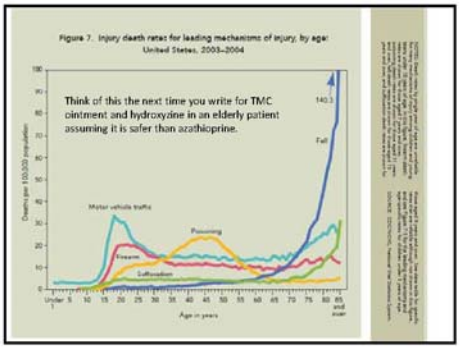
What do we know about the risks of immunosuppressive agents?

- Malignancy
  - Single agent treatment for less than 2 years – little data to support substantial risk
    - Confounders – multiple agents used in transplant setting, viral mediated tumors (clear link but rare), background risk in disease treated (e.g. –RA)
  - Limited studies which are directly applicable to the practice of dermatology
    - Known carcinogens such as UVL appear to generate limited concern

Overall and cancer related mortality among patients with ocular inflammation treated with immunosuppressive drugs: retrospective cohort study

Kempen, et al 2010 - BMJ





Why I like to use azathioprine

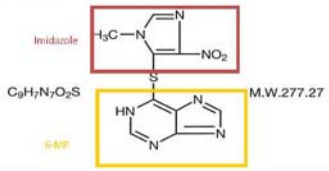
- I find it effective for many inflammatory skin diseases
  - Eczema, urticarial dermatitis, lichen planus, bullous pemphigoid, pemphigus
- Relatively inexpensive
- Can use single daily dosing and have few concerns about timing of administration (unlike MMF)
- Precise monitoring tools available which allow for aggressive dosing
- Large experience in other inflammatory diseases
- Can use for extended periods of time without metabolic or toxic effects

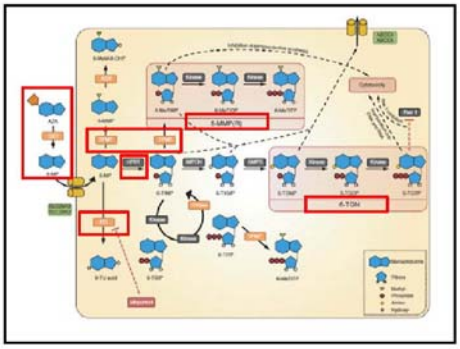
Azathioprine - Thiopurines

- Initially developed in 1960's and used for organ transplants
- Prescribed subsequently for a host of inflammatory and autoimmune diseases
- Used singly or along with systemic corticosteroids

Azathioprine - Pharmacology

- AZA is a pro-drug
  - Imidazole derivative of 6-mercaptopurine (6-MP)
  - Rapidly converted (half-life 3 hours) to 6-MP
  - Metabolized via three pathways





AZA: Clinical uses

- FDA approved for
  - Kidney transplant rejection prophylaxis
  - Rheumatoid arthritis, severe
  - Crohn's disease
  - Ulcerative colitis
- Off label dermatology uses –personal experience using
  - Immunobullous diseases
  - CTD diseases – LE, DMM, small vessel vasculitis
  - Psoriasis, lichen planus, and eczematous diseases
  - Photodermatoses
  - Urticaria and urticarial dermatitis
  - Other pruritic and oral corticosteroid responsive diseases
  - Virtually all steroid responsive skin diseases

Table 1 Licensed and unlicensed indications for azathioprine in the treatment of dermatological disorders (in Great Britain)

Licensed indications	Unlicensed indications
Systemic lupus erythematosus	Atopic dermatitis
Dermatomyositis	Psoriasis
Pemphigus vulgaris	Bullous pemphigoid
	Chronic actinic dermatitis
	Pyoderma gangrenosum
	Pityriasis rubra pilaris
	Wegener's granulomatosis
	Cutaneous vasculitis

bullous pemphigoid (Grade B; level IV)
Pemphigus vulgaris (Grade B; level II)
Severe, recalcitrant atopic dermatitis (Grade A; level I)
Chronic actinic dermatitis (Grade A; level I)
Behcet's disease (Grade A; level I)
Severe, recalcitrant psoriasis (Grade C; level IV).
Wegener's granulomatosis, pyoderma gangrenosum, pityriasis rubra pilaris,lupus erythematosus, and lichen planus (anecdotal- Grade C; level IV).

AZA: Deployment and Monitoring

- Baseline: TPMT, CMP, CBC (+/-pregnancy test),
  - *PPD (or Interferon gamma release assay), Hep B, C Serology, HIV*
- CMP, CBC bimonthly for 2 months then q3-6 months
- Complete skin exams if on AZA for more than 2 years in patients predisposed to skin cancer

Thiopurine methyltransferase activity

Table 1. Interethnic variation of TPMT activity

Group	N	Homozygous wild-type (%)	Heterozygote (%)	Homozygous mutation (%)	TPMT*2 (%)	TPMT*3A (%)	TPMT*3C (%)
American Caucasians	Calculated	92.5	7.4	0.14	0.2	3.2	0.2
British Caucasians	199	89.9	9.6	0.5	0.5	4.5	0.3
French Caucasians	191	85.9	13.6	0.5	0.5	5.7	0.8
African Americans	Calculated	90.7	9.2	0.2	0.4	0.8	2.4
South Asians	99	98	2	0	0	1	0
Ghanaians	217	85.3	14.4	0.5	0	0	7.6
Kenyans	101	89.1	10.9	0	0	0	5.4
Chinese	192	95.3	4.7	0	0	0	2.3
Japanese	553	97.3	2.4	0.4	0	0	1.5
Thai	75	89	11	0	0	0	5.3

Modified from McLeod.[40]

- Two approaches to measurement
  - RBC activity
  - genotypes
- Reason to check TPMT
  - Dosing
  - Avoidance of TPMT nulls

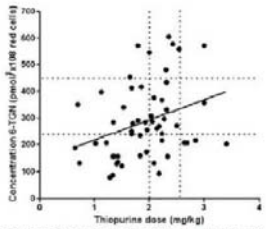


FIGURE 1. Relationship of the 6-TGN concentrations with the thiopurine dose. The 6-MP dose was calculated using a conversion factor of 2.0731. The known noncompliant patients and two outlier results were omitted. A weak correlation was present on regression analysis ($r = 0.32$; $P = 0.018$; Pearson's regression). The broken lines represent the weight-based recommended dosage (x-axis) and therapeutic range for 6-TGN (y-axis).

AP&T Alimentary Pharmacology and Therapeutics

Review article: the benefits of pharmacogenetics for improving thiopurine therapy in inflammatory bowel disease

L. Chouchana[*,†,‡], C. Narjoz[*,†,‡], P. Beaune[*,†,‡], M.-A. Loriot[*,†,‡] & X. Roblin[§]

Conclusions
Based on the literature data, we provide a therapeutic algorithm for thiopurines therapy with starting dose recommendations depending on TPMT status and thereafter dose adjustments according to five metabolite profiles identified with therapeutic drug monitoring (TDM). This algorithm allows a dosage individualisation to optimise the management of patients under thiopurine. Furthermore, identification of new pharmacogenetic biomarkers is promising for ensuring maximal therapeutic response to thiopurines with a minimisation of the risk for adverse events.

Aliment Pharmacol Ther 2012; 35: 15–36

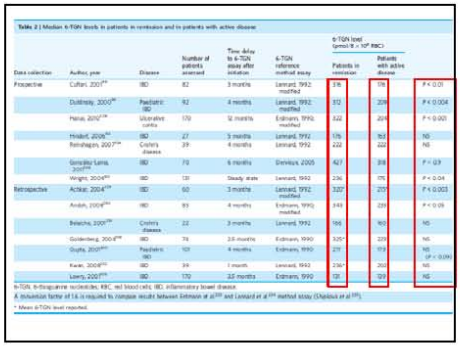
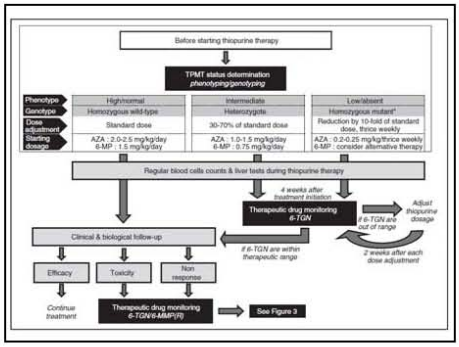


Table 2 | Median 6-TGN levels in patients in remission and in patients with active disease

Data collection	Author, year	Disease	Number of patients assessed	Time delay to 6-TGN assay after initiation	6-TGN reference method assay	6-TGN level (pmol/8 × 10⁸ RBC): Patients in remission	Patients with active disease	
Prospective	Cuffari, 2001[44]	IBD	82	3 months	Lennard, 1992 modified	316	156	P < 0.01
	Dubinsky, 2000[46]	Paediatric IBD	92	4 months	Lennard, 1992 modified	372	239	P < 0.004
	Haraz, 2012[134]	Ulcerative colitis	170	12 months	Erdmann, 1990; modified	322	204	P < 0.003
	Hindorf, 2006[45]	IBD	27	3 months	Lennard, 1992	176	163	NS
	Reinshagen, 2007[135]	Crohn's disease	39	4 months	Lennard, 1992	222	222	NS
	González Lama, 2007[136]	IBD	70	6 months	Dervieux, 2005	427	318	P < 0.9
	Wright, 2004[137]	IBD	131	Steady state	Lennard, 1992	236	75	P < 0.04
Retrospective	Achkar, 2004[138]	IBD	60	3 months	Lennard, 1992 modified	320*	270*	P < 0.003
	Andoh, 2004[139]	IBD	83	4 months	Erdmann, 1990; modified	348	285	P < 0.05
	Belaiche, 2001[140]	Crohn's disease	22	3 months	Lennard, 1992	166	163	NS
	Goldenberg, 2004[141]	IBD	78	2.5 months	Erdmann, 1990	325*	229*	NS
	Gupta, 2007[142]	Paediatric IBD	101	4 months	Erdmann, 1990	237	173	NS (P = 0.09)
	Kwan, 2004[143]	IBD	34	1 month	Lennard, 1992	230*	202*	NS
	Lowry, 2007[144]	IBD	170	2.5 months	Erdmann, 1990	281	220	NS

6-TGN, 6-thioguanine nucleotides; RBC, red blood cells; IBD, inflammatory bowel disease.
A conversion factor of 1.6 is required to compare results between Erdmann et al.[139] and Lennard et al.[134] method assay (Dubinsky et al.[46]).
* Mean 6-TGN level reported.



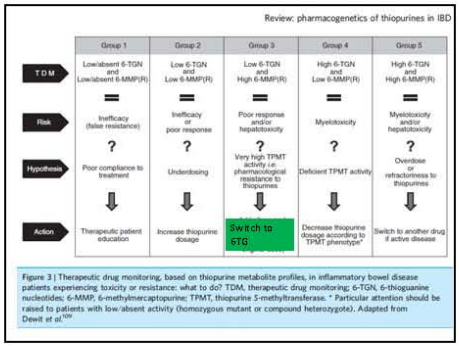


Figure 3 | Therapeutic drug monitoring, based on thiopurine metabolite profiles, in inflammatory bowel disease patients experiencing toxicity or resistance: what to do? TDM, therapeutic drug monitoring; 6-TGN, 6-thioguanine nucleotides; 6-MMP, 6-methylmercaptopurine; TPMT, thiopurine S-methyltransferase. * Particular attention should be raised to patients with low/absent activity (homozygous mutant or compound heterozygote). Adapted from Dewit et al.[106]

AZA and itch

- Few trials separately analyze response to itch
  - Atopic dermatitis trials – use SCORAD or VAS
- Only one dermatitis trial measured TP levels
  - JAAD Aug 2012 – 12 pediatric patients – only three had 6TG levels within the therapeutic range
  - Used SCORAD measure – 1/3 weighted for itch

Reasons for AZA failure

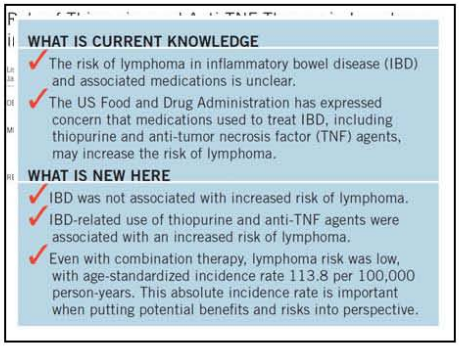
- Acute intolerance – random event seen within fist 10-20 days
- Delayed intolerance – toxic 6MMP levels
  - Malaise and nausea even with LFT elevations
- Inadequate dosing – failure to attain significant 6TG levels
- Leukopenia/cytopenias without efficacy – seen mostly in elderly patients

Azathioprine Complications - Common

- Intolerance syndrome – within first 2-4 weeks
  - Think of pancreatitis (get serum lipase)
- Hepatitis – associated with increased 6-MMP levels
- Bone marrow suppression – associated with increased 6-TG levels
- Squamous cell CA of skin – long term use

Azathioprine complications- uncommon

- Pancreatitis - ~1:600
- Infections
- Lymphoma
- Leukemia
- Other malignancies
- How large is the risk?????
- How to explain the risk?



WHAT IS CURRENT KNOWLEDGE

- ✓ The risk of lymphoma in inflammatory bowel disease (IBD) and associated medications is unclear.
- ✓ The US Food and Drug Administration has expressed concern that medications used to treat IBD, including thiopurine and anti-tumor necrosis factor (TNF) agents, may increase the risk of lymphoma.

WHAT IS NEW HERE

- ✓ IBD was not associated with increased risk of lymphoma.
- ✓ IBD-related use of thiopurine and anti-TNF agents were associated with an increased risk of lymphoma.
- ✓ Even with combination therapy, lymphoma risk was low, with age-standardized incidence rate 113.8 per 100,000 person-years. This absolute incidence rate is important when putting potential benefits and risks into perspective.

Thioprurines and Skin Cancer

- Gastroenterology. 2011 Nov;141(5):1621-28.e1-5. Epub 2011 Jun 25.
- Prospective observational cohort study of 19,486 patients with IBD, enrolled from May 2004 to June 2005, who were followed up until December 31, 2007
  - Median FU ~ three years

Thioprurines and Skin Cancer

- Increased risk particularly in older patients and duration of treatment
- In the over 19 patients enrolled, there we a total of 32 cancers
  - Five in never treated with thiopurines (10,810 patients in pool)
  - Nine in patients previously treated (2809 patients in pool)
  - 18 in patient currently receiving (5867patients in pool) - highest risk = approximately one skin cancer per 1000 patient years.
  - If you had 500 patients on AZA, you would expect 1 extra skin cancer every two years of treatment in that population

Azathioprine - Summary

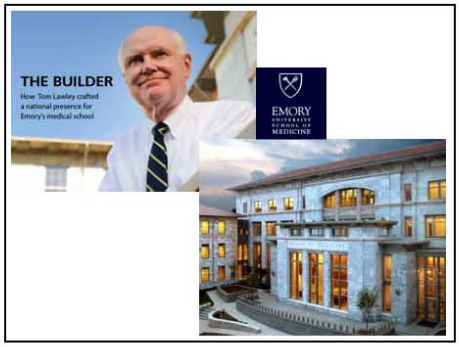
- AZA and related thiopurines have been used in medicine for more than 50 years
- AZA appears to be useful for the treatment of a variety of inflammatory diseases, including diseases of the skin
- New tools for the measurement of active drug levels allows for more precise dosing to avoid treatment failure and toxicity
- The final decision to use agents such as AZA requires shared decision making between patient and physician.

Alternative agents

- Cyclosporine – not a remittive agent and poorly tolerated in those over age 40 at doses needed to deal with inflammatory itch
  - Similar issues with tacrolimus – poor absorption
- Methotrexate – little personal experience.
- MMF – more expensive (generic only marginally more), more difficult to take (without food, multiple daily doses), less dosing flexibility and fewer management tools
- Recommendations are based upon personal experience, not hard data

Summary

- Itch is a major source of morbidity in skin disease and not optimally treated
- Many patients itch as a consequence of inflammatory skin disease
- Systemic treatment with anti-inflammatory agents may benefit patients with pruritus
- Azathioprine may be a useful agent for treatment of pruritus since it is modestly priced, can be managed using new monitoring tools, and we have relatively good safety and tolerance data



Pathogenesis of Dermatitis Herpetiformis: A Model for Gut-Associated Skin Diseases

Russell Hall, MD

DERMATITIS HERPETIFORMIS: The Skin and The GUT

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Conflict of Interest Disclosure

There are no actual or potential conflict of interest in relation to this presentation.

DERMATITIS HERPETIFORMIS

- Chronic, median age of onset - 3rd decade (? lifelong).
- Grouped vesicles or urticaria-like eruption primarily located on extensor surfaces - accompanied by intense itching and burning.
- Dramatic response to sulfones or sulfapyridine.
- Patients have an associated, most often asymptomatic, gluten-sensitivity enteropathy.

DERMATITIS HERPETIFORMIS

- Extremely itchy vesicles and eroded papules on elbows, knees, buttock and other extensor surfaces
- Histology
  - Subepidermal blister with neutrophils at the dermal papillary tips(microabscesses)
  - No associated small vessel vasculitis
- Direct Immunofluorescence
  - Granular IgA deposits at the basement membrane in the dermal papillary tips

DERMATITIS HERPETIFORMIS Treatment

Dapsone and Sulfapyridine

Itching and new lesions stop within 12 hours to 2 days after institution of sulfone or sulfapyridine therapy - lesions

Symptoms recur 24 - 72 hours after discontinuing drugs

Dosage of Dapsone Required to Treat Dermatitis Herpetiformis

Dapsone Dosage

<25*	50-75	100-200	200-275	300-400
1**	11	15	8	4

* Mg/day

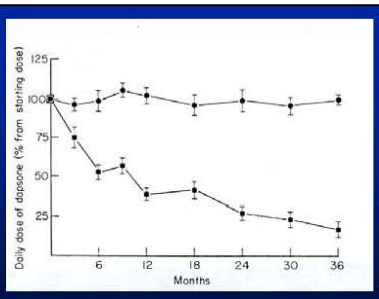
** # patients

DERMATITIS HERPETIFORMIS

- **Small bowel biopsies show villous atrophy**
  Marks J et al, Lancet, 1966
- **Intestinal lesions found to be gluten sensitive enteropathy**
  Fry L et al, Lancet 1967
  Shuster S et al, Lancet 1968
- **Most patients have no GI complaints (approx 10% with mild symptoms)**

DERMATITIS HERPETIFORMIS
Treatment 1965-1975

- "The dose of dapsone needed to control the rash did not decrease in any of the patients during the period of gluten withdrawal (9m-7yr)." Shuster, Watson, Marks J, Lancet, 1968
- "At the end of this time (6 m) 4 (of 7) patients had improved substantially"
  Fry, McMinn, Cowan, Hoffbrand, Lancet, 1968
- "12 patients needed less dapsone to control their skin complaint..." Marks, R, ,Whittle, Br Med J, 1969
- "We believe indeed that none of the published evidence shows that the rash, in contrast to the enteropathy, of dermatitis herpetiformis is improved by gluten withdrawal"
  Marks J, Shuster , Br Med J, 1970



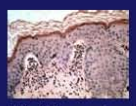
Reunala et al, Br J Dermatol, 1977

DERMATITIS HERPETIFORMIS
Treatment

- **Dapsone and Sulfapyridine**
  Itching and new lesions stop within 12 hours to 2 days after institution of sulfone or sulfapyridine therapy - lesions
  Symptoms recur 24 - 72 hours after discontinuing drugs
  Small bowel does not improve
- **Gluten Free Diet**
  Lesions and symptoms also respond to dietary gluten withdrawal , often the sulfones or sulfapyridine can be discontinued.

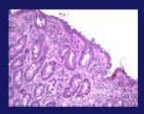
Pathogenesis of Dermatitis Herpetiformis

Papules and vesicles on extensor surfaces



Neutrophilic infiltrate at the papillary tips

Granular IgA at the dermal-epidermal junction



Gluten Sensitive Enteropathy

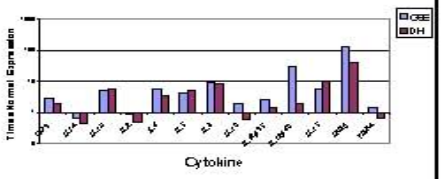
HYPOTHESIS:

The nature of the mucosal immune response to wheat protein in the gut of patients with DH is different from that seen in patients with isolated GSE, resulting in different clinical disease.

Small Bowel Immune Response in DH and isolated GSE

What is the pattern of the cytokine response in the gut of patients with DH compared to those with isolated GSE and to normal subjects?

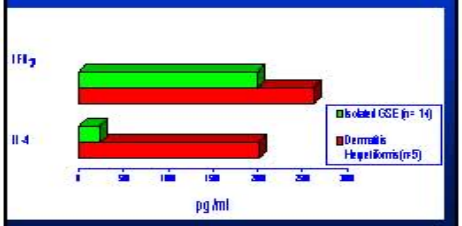
Cytokine mRNA Expression Small Bowel Biopsy DH and GSE



Small Bowel Cytokine Expression DH and Isolated GSE

- What is the response to maximal stimulation of Gut T cells?
- Small bowel biopsies were obtained from 4 patients with DH and 10 patients with isolated GSE
- All of the DH patients were on gluten containing diets
- 9/10 isolated GSE patients were on gluten free diets

Gut T Cell Lines Cytokine Production: DH and Isolated GSE



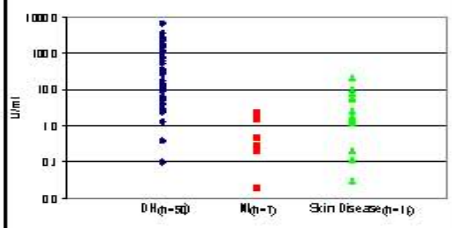
Small Bowel Cytokine Expression DH and Isolated GSE

- Gut biopsies from both DH and isolated GSE patients have increased expression of IL1β, IL-4, IL-8, IL-12, IFN-γ demonstrating ongoing mucosal immune response
- Lack of GI symptoms in DH allows for ongoing gluten ingestion, promoting an ongoing, low grade mucosal immune response

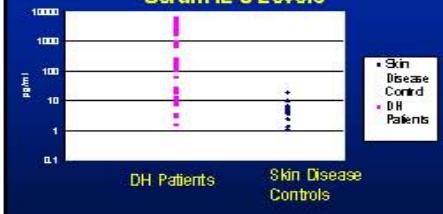
Serum Markers of Gut Immune Response in Dermatitis Herpetiformis

- Gut biopsies show increased expression of IL-8 and IFN-γ mRNA
- Is there evidence in the sera of patients with DH of ongoing mucosal immune response?

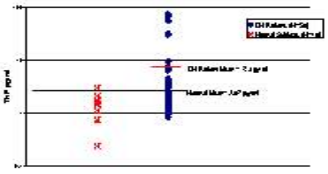
Serum IgA anti-Tissue Transglutaminase



Serum IL-8 Levels



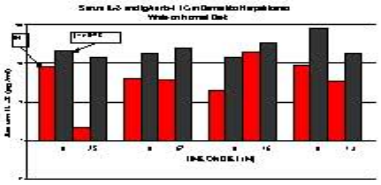
Increased serum TNF-α in patients with DH

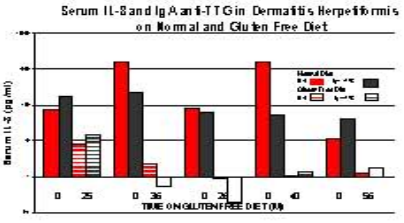


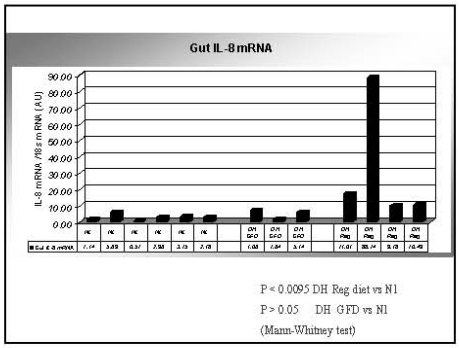
Dermatitis Herpetiformis

Serum Markers of Gut Immune Response

- Patients with DH and skin disease controlled by dapsone have evidence of ongoing inflammatory disease
  - Elevated IgA anti-tissue transglutaminase
  - Elevated IL-8 levels
  - Elevated sE-selectin
  - Elevated TNF-α
- Is this inflammatory response related to a gut response to wheat?

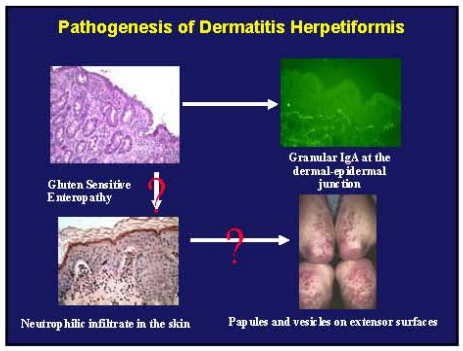


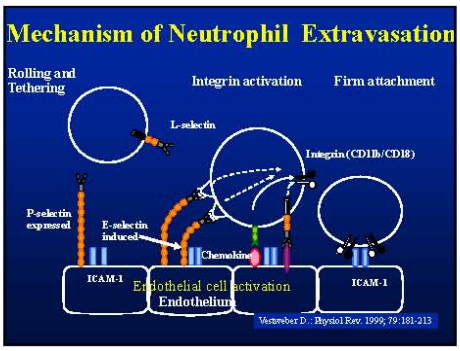




Systemic Manifestations of the mucosal immune response in DH

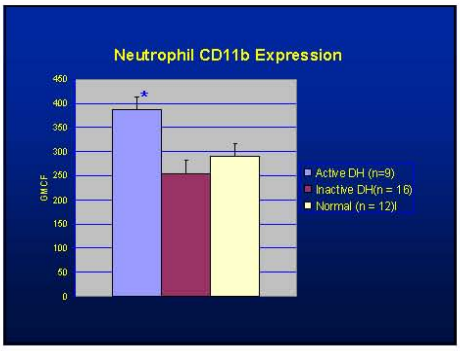
- Patients with DH have increased serum IL-8, sE-selectin, TNF-α and IgA anti-TTG
- Adherence to a gluten free diet diet results in reduction in both serum IL-8 and IgA-anti-TTG levels
- Small bowel biopsies of patients on regular diet have increased expression of IL-8 mRNA compared to normal subjects
- Small bowel biopsies of patients on gluten free diets have no increased expression of IL-8 mRNA



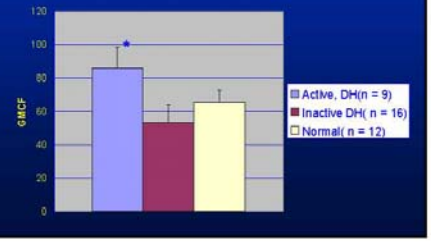


Neutrophil Migration in DH Hypothesis

- Ongoing mucosal immune response in the gut produces cytokines (IL-4, IL-8, IFN-γ) that partially primes circulating neutrophils (increase expression of CD11b, increase function FcIgA receptors)

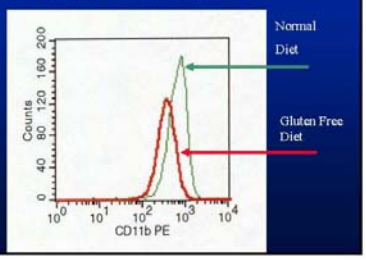


IgA Neutrophil Binding Capacity



CD11b Expression on Neutrophils in Dermatitis Herpetiformis

Pre - and Post Gluten Free Diet



Characterization of Neutrophils in Dermatitis Herpetiformis

- Circulating neutrophils were studied in patients with DH on gluten containing diet and dapsone.
- Circulating neutrophils from patients with DH showed an increased expression of CD11b with decreased expression of L-selectin.
- Neutrophils in patients with DH on gluten containing diets have increased function of Fc IgA receptors

Dermatitis Herpetiformis

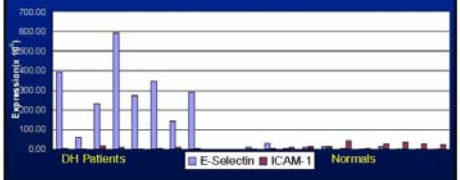
Endothelial Cell Activation in the Skin

- Extravasation of neutrophils into skin requires both neutrophil and endothelial cell activation
- Elevated serum cytokines and inflammatory mediators may activate endothelial cells in the absence of local skin 'injury'

E-Selectin and ICAM-1 Expression

DH and Normal Subjects

Inner Arm Skin



Dermatitis Herpetiformis: Pro-Inflammatory Events

- Increased level of IL-8, TNF-α in serum of patients with DH
- Increased expression of E-selectin mRNA in normal skin of patients with DH
- Circulating neutrophils show evidence of increased expression of CD11b consistent with partial priming

Pathogenesis of Dermatitis Herpetiformis

Neutrophil Migration in DH Hypothesis

- Ongoing mucosal immune response in the gut produces cytokines (IL-4, IL-8, IFN-γ) that partially primes circulating neutrophils (increase expression of CD11b, increase function FcIgA receptors)
- During development of skin lesions, local production of cyto-chemokines complete priming of neutrophils (shedding L-selectin)
- Neutrophils migrate into skin, bind IgA and skin lesions develop

Hypothesis

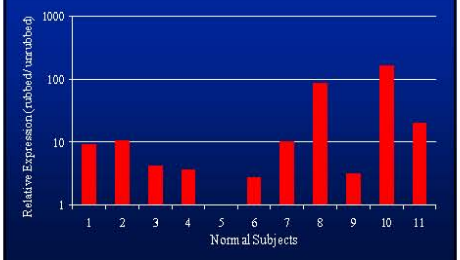
- Minor trauma to skin, such as that which occurs on extensor surfaces of the skin, will result in the increased expression of E-selectin and cytokines.
- This increased expression of E-selectin and cytokines in the skin could, in the presence of activated neutrophils, result in the development of skin lesions in patients with DH at the site of injury.

Cytokine and Adhesion Protein Gene Expression

Normal and Rubbed Skin

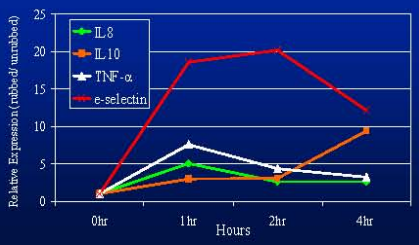
- Inner Arm Skin of normal subjects rubbed gently for 2 minutes with pencil eraser
- 4 hours after rubbing, 4 mm punch biopsy taken of rubbed and unrubbed skin
- Total RNA isolated, cDNA produced

E-selectin Expression at 4 hrs



Time Course

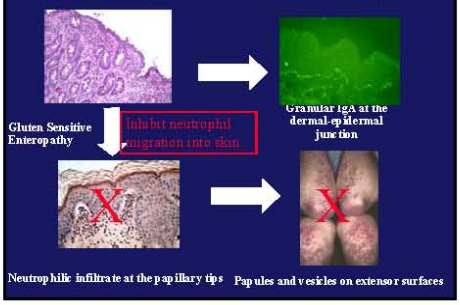
Cytokine Expression after minor trauma



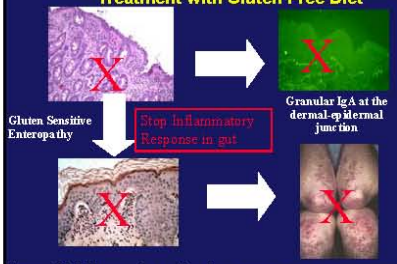
Summary

- Minor trauma to normal inner arm skin by rubbing resulted in an increased expression of E-selectin, IL-8 and IL-10 mRNA when compared to normal, unrubbed skin.
- Increased expression of E-selectin and IL-8 and IL-10 mRNA was seen as early as 1 hour after trauma.
- E-selectin protein was seen in the skin 4 hours after rubbing in normal subjects with no evidence of an inflammatory infiltrate.

Dermatitis Herpetiformis: Treatment with Dapsone



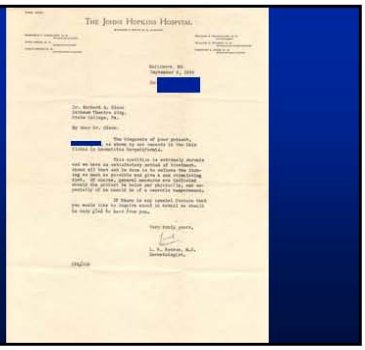
Free Diet Dermatitis Herpetiformis: Treatment with Gluten Free Diet

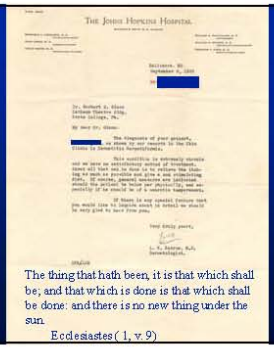


Pathogenesis of Dermatitis Herpetiformis

Mucosal Inflammation and Skin "The DH Model"

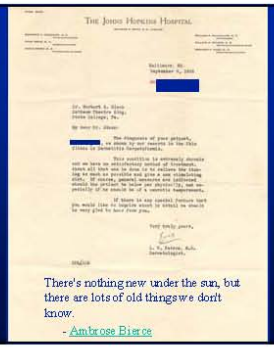
- Ongoing low grade inflammation in the gut may result in systemic cytokines which 'prime' the skin and perhaps other organs(joints)
- Ongoing low grade inflammation in the gut primes circulating inflammatory cells (PMNs, lymphocytes, macrophages)
- Local trauma (pathergy) stimulates local cytokines leading to skin lesions (Erythema nodosum, pyoderma gangrenosum, Sweet's Syndrome, Bechet's)
- Treatment of gut inflammation may improve 'idiopathic' inflammatory skin diseases





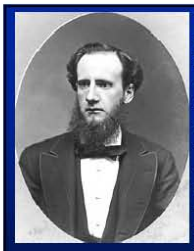
The thing that hath been, it is that which shall be; and that which is done is that which shall be done: and there is no new thing under the sun.

Ecclesiastes (1, v. 9)



There's nothing new under the sun, but there are lots of old things we don't know.

- Ambrose Bierce



Louis Duhring

1845-1913

The skin and subcutaneous tissue, composing the integument, should be regarded as part of the body, rather than as an independent organ. The skin possesses the closest relations with the general economy, as shown by the observation that there are comparatively few so-called general diseases in which it . . . is not at some period involved in a slight or marked degree.

Cutaneous Medicin. Pt. 1, Preface.

Collaborators

Dermatology

Robert Streilein — Clark Otley
Maureen Keough — Bita Bagheri
Sylvia Owen — Clinzo Mickle
Fumiko Takeuchi — Khaled Hassan
Keith Benbinisty — Arash Roneghy

Gastroenterology

Alastair Smith — John Baillie
Cynthia Rudert — Joanne Wilson
Kenneth Cochrane

Acknowledgments

- National Institutes of Health
- Dermatology Foundation
- Patients with Dermatitis Herpetiformis and Gluten sensitive enteropathy

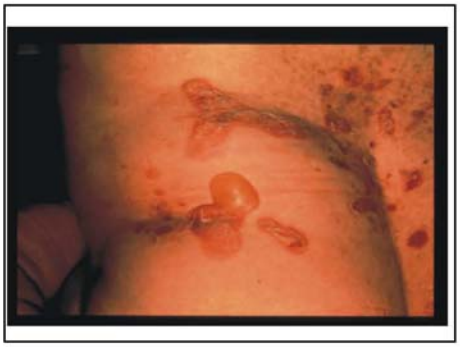
Pathophysiology and Therapeutic Implications from Cloning Pemphigus

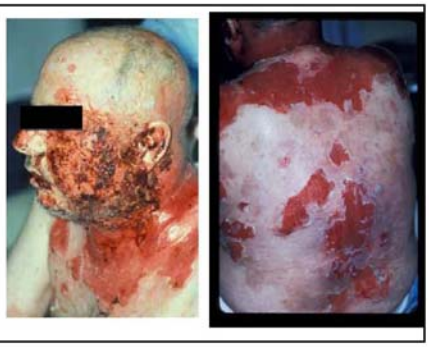
John Stanley, MD

Therapeutic and Pathophysiologic Implications of Cloning Pemphigus Antibodies

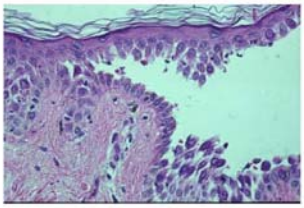
Types of pemphigus

- Pemphigus vulgaris
- Pemphigus foliaceus

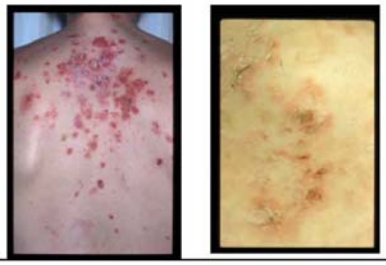




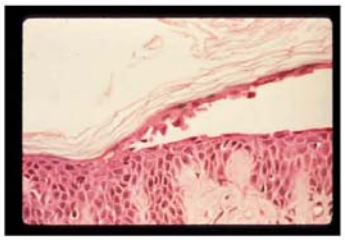
PV: histology



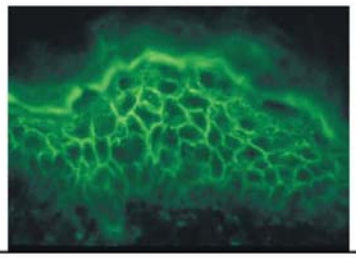
PF



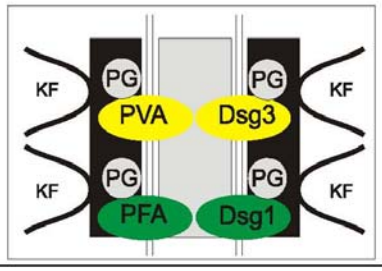
PF: histology



Pemphigus: IIF



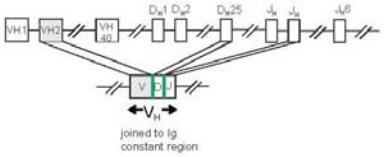
Desmosome



Insights from cloning pemphigus mAbs

- Monovalent anti-Dsg mAb causes disease
- Patients have both pathogenic and non-pathogenic antibodies
- The pathogenic antibody response is genetically restricted and oligoclonal
- Pathogenic antibodies share homologous amino acid sequences among patients
- There are therapeutic implications of the oligoclonal B cell response

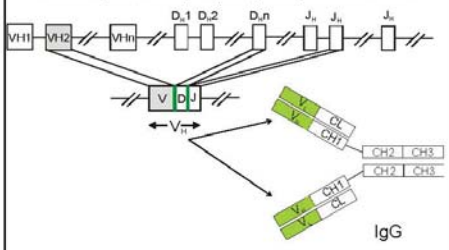
DNA recombination in B cell to produce antibody

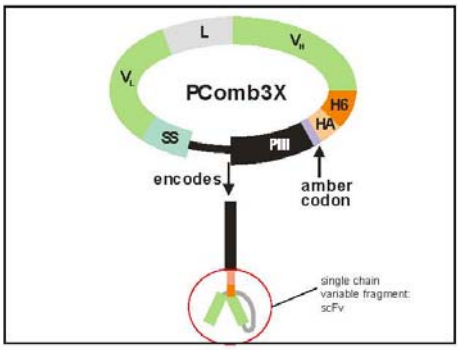


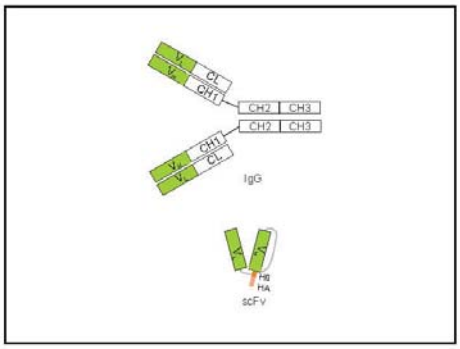
Each B cell produces a unique V_H and V_L chain by DNA recombination

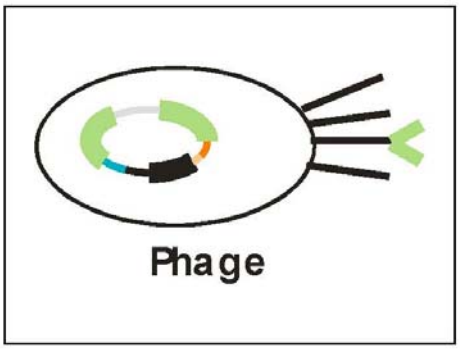
DNA recombination in B cell to produce antibody

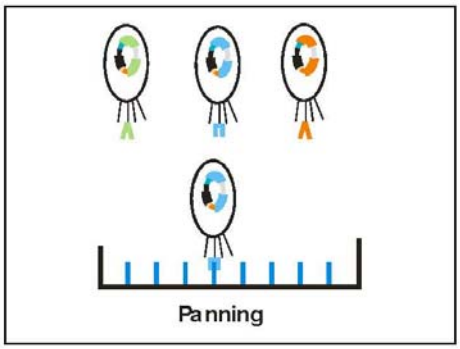
Each B cell produces a unique V_H and V_L chain by DNA recombination

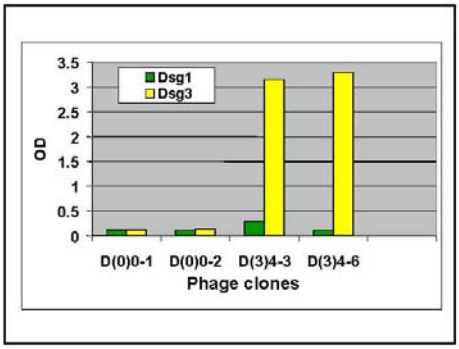


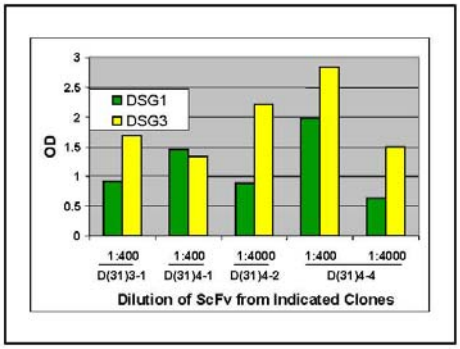

L
V_H
V_L
PComb3X
H6
HA
SS
PIII
encodes
amber codon
single chain variable fragment: scFv

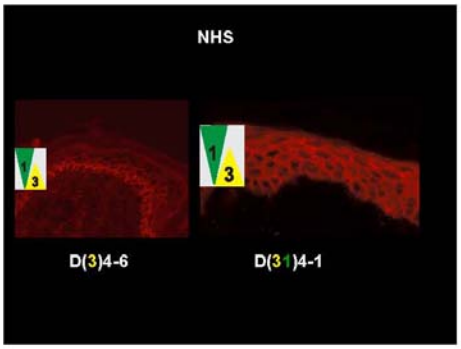

IgG
scFv

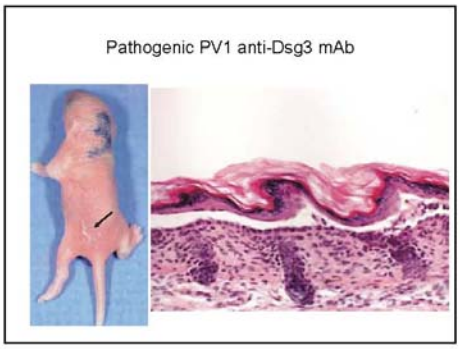

Phage

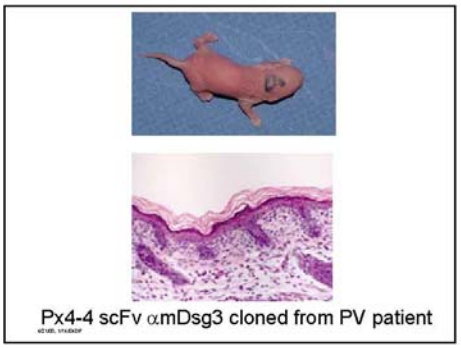

Panning

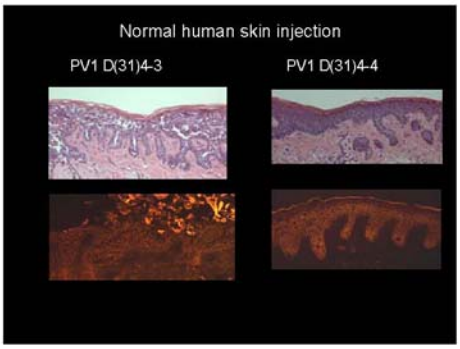

Dsg1
Dsg3
OD
3.5
3
2.5
2
1.5
1
0.5
0
D(0)0-1
D(0)0-2
D(3)4-3
D(3)4-6
Phage clones

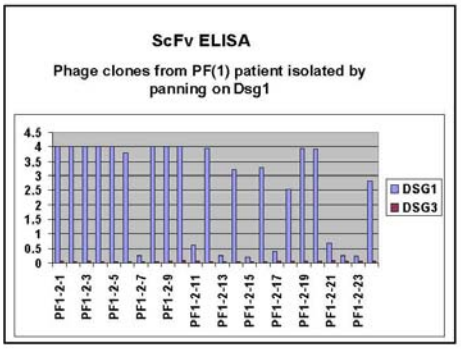

DSG1
DSG3
OD
3
2.5
2
1.5
1
0.5
0
1:400
D(31)3-1
1:400
D(31)4-1
1:4000
D(31)4-2
1:400
1:4000
D(31)4-4
Dilution of ScFv from Indicated Clones

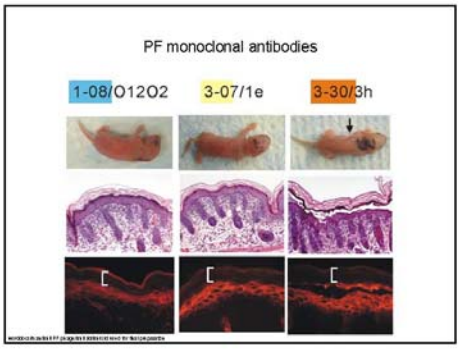

NHS
D(3)4-6
D(31)4-1


Pathogenic PV1 anti-Dsg3 mAb

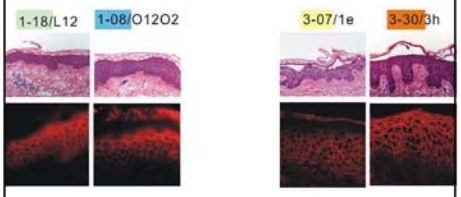

Px4-4 scFv αmDsg3 cloned from PV patient


Normal human skin injection
PV1 D(31)4-3
PV1 D(31)4-4

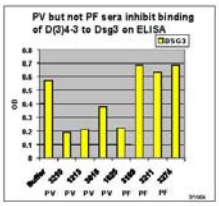

ScFv ELISA
Phage clones from PF(1) patient isolated by panning on Dsg1
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
DSG1
DSG3
PF1-2-1
PF1-2-3
PF1-2-5
PF1-2-7
PF1-2-9
PF1-2-11
PF1-2-13
PF1-2-15
PF1-2-17
PF1-2-19
PF1-2-21
PF1-2-23


PF monoclonal antibodies
1-08/O12O2
3-07/1e
3-30/3h

PF monoclonal antibodies injected into normal human skin



Human pemphigus sera share epitopes with pathogenic mAb from a PV patient



Use of VH genes in pathogenic and non-pathogenic pemphigus mAbs

Pathogenic:

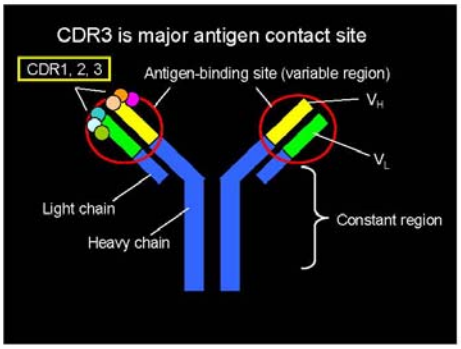
- PV
  - VH1-69*
  - VH3-07
  - VH1-46
  - VH1-69
  - VH1-46
  - VH1-46
  - VH4b
- PF
  - VH3-30
  - VH3-53

Non-pathogenic:

- PV
  - VH4-04
  - VH1-e
  - VH1-69*
  - VH3-08
  - VH1-46
  - VH5-51
  - VH1-69*
  - VH1-69
  - VH5a
- PF
  - VH1-18
  - VH1-08
  - VH3-09
  - VH3-07
  - VH4-4
  - VH3-30
  - VH3-66
  - VH1-08
  - VH3-09

- VH gene does not specify pemphigus pathogenicity
- Is there a common feature of CDR3s in causing pathogenicity?

CDR3 is major antigen contact site



Most pathogenic PV and PF mAbs share a CDR3 consensus amino acid sequence: D/E-x-x-x-W

PV1	VH3-07	YYCAS-----GGVVDFDHWGQ
PV1	VH1-46	YYCARD----RQGFDLDVWGQ
PV3	VH1-46	YYCARD----LGGFDFDYWGQ

Most pathogenic PV and PF mAbs share a CDR3 consensus amino acid sequence: D/E-x-x-x-W

PV1	VH3-07	YYCAS-----GGVVDFDHWGQ
PV1	VH1-46	YYCARD----RQGFDLDVWGQ
PV3	VH1-46	YYCARD----LGGFDFDYWGQ
PF2	VH3-53	YYCVR----GPAYYDIDYWGQ

Most pathogenic PV and PF mAbs share a CDR3 consensus amino acid sequence: D/E-x-x-x-W

PV1	VH3-07	YYCAS-----GGVVDFDHWGQ
PV1	VH1-46	YYCARD----RQGFDLDVWGQ
PV3	VH1-46	YYCARD----LGGFDFDYWGQ
PF2	VH3-53	YYCVR----GPAYYDIDYWGQ
PV1	VH1-69	YYCAR-------GGDYSGWYNFDYWGQ
PF1	VH3-30.3	YYCAR------DRVEGYVWGGTFDHWGQ

Most pathogenic PV and PF mAbs share a CDR3 consensus amino acid sequence: D/E-x-x-x-W

PV1	VH3-07	YYCAS-----GGVVDFDHWGQ
PV1	VH1-46	YYCARD----RQGFDLDVWGQ
PV3	VH1-46	YYCARD----LGGFDFDYWGQ
PF2	VH3-53	YYCVR----GPAYYDIDYWGQ
PV1	VH1-69	YYCAR-------GGDYSGWYNFDYWGQ
PF1	VH3-30.3	YYCAR------DRVEGYVWGGTFDHWGQ
AK23	mouse	YYCAR------GGYDGYPWGQ

Most pathogenic PV and PF mAbs share a CDR3 consensus amino acid sequence: D/E-x-x-x-W

PV1	VH3-07	YYCAS-----GGVVDFDHWGQ
PV1	VH1-46	YYCARD----RQGFDLDVWGQ
PV3	VH1-46	YYCARD----LGGFDFDYWGQ
PF2	VH3-53	YYCVR----GPAYYDIDYWGQ
PV1	VH1-69	YYCAR-------GGDYSGWYNFDYWGQ
PF1	VH3-30.3	YYCAR------DRVEGYVWGGTFDHWGQ
AK23		YYCAR------GGYDGYPWGQ
PV2	VH1-69	YYCARDRMRFQESEGFDYWGQ
PV3	VH1-46	YYCARD-----QSLGMDVWGQ
PV1	VH4b	YYCAR---TTTAYMYFDLWGR

7/10 pathogenic anti-Dsg antibodies share CDR3 consensus

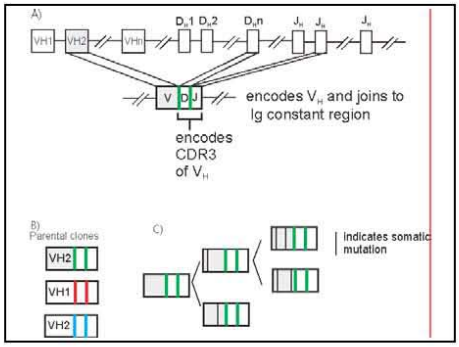
0/16 non-pathogenic pemphigus antibodie have consensus

Therapeutic Implications

- Pemphigus antibodies share similarities in their CDR3 regions and in the epitopes they bind
  - Screen peptide or small molecule libraries for pathogenic blockers

Do patients maintain the same non-tolerant B cell clones throughout the course of their disease?

Implication: if so, then eliminating these clones should cure disease

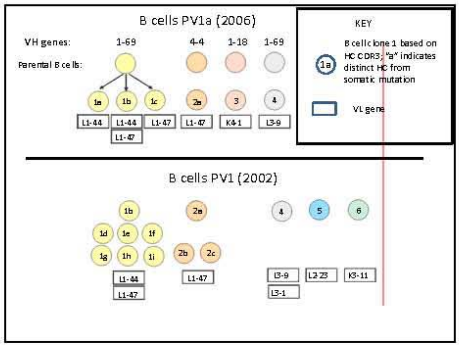


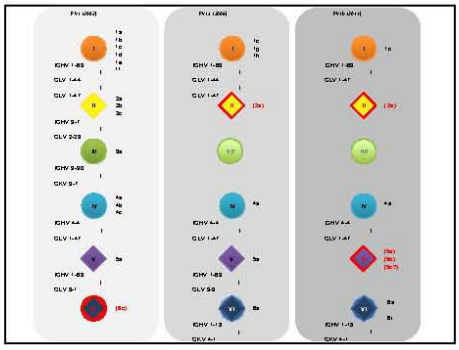
Oligoclonal B cell response in pemphigus
Unique anti-Dsg3 Vh B cell clones from each patient

Patient	Clone#	Name	VH gene	CDR3	Patho?
PV1	1	4B1	1-69	DRAAYYESGYYYIGDFW	No
	2	4B3	3-07	SGGVVDFDNW	Yes
	3	3B12	3-30	EALVYYDSSGYYKGGFDY	?
	4	Px4-3	1-69	GGDYSGWNFDYW	Yes
	5	Px4-4	4-4	GWDRTGPRGVPSHWYFDLW	No
PF1	1	PF1-2-05	1-18	GVGSGNWDYW	No
	2	PF1-2-22	1-08	GLPPGVVTKPNYYYYAMDVW	No
	3	PF1-8-02	3-07	ESPYYSSGTVPDFW	weak
	4	PF1-8-15	3-30	DRVDGYVAGTFDSW	Yes
PF2	1	F23-5	1-08	GRTVRPGELPVSEGGMDVW	No
	2	F24-2	3-30	QGWVIETSGIRASGFDVW	No
	3	F24-9	3-53	GPAYYDIDYW	Yes
	4	F24-15	3-66	EGGGLTIDYW	No

PV1a (2006) compared to PV1 (2002)
Phage Cloning Variable Heavy Chain Analysis

PV1a Phage clone name	VH gene (IGHV)	B cell clonal origin	V_H*	HC CDR3	PV1 phage clones with same B cell clonal origin	PV1 phage clones with HC exact match	Duplicate phage clone (HC and LC) in PV1
4-1	1-69	1	1a	CARDKAAYYEAGYYYIGDFWG	4B-1/2/5/7 and 3B 3/8/9	none	none
4-5	1-69	1	1b	CARDKAAYYESGYYYIGDFWG	4B-1/2/5/7 and 3B 3/8/9	4B-7	none
4-8	1-69	1	1b	CARDKAAYYESGYYYIGDFWG	4B-1/2/5/7 and 3B 3/8/9	4B-7	none
4-11	1-69	1	1b	CARDKAAYYESGYYYIGDFWG	4B-1/2/5/7 and 3B 3/8/9	4B-7	none
3-12	1-69	1	1b	CARDKAAYYESGYYYIGDFWG	4B-1/2/5/7 and 3B 3/8/9	4B-7	none
3-2D	1-69	1	1b	CARDKAAYYESGYYYIGDFWG	4B-1/2/5/7 and 3B 3/8/9	4B-7	none
3-11	1-69	1	1c	CARDKAAYYESGYYYIGDFWG	4B-1/2/5/7 and 3B 3/8/9	none	none
4-3	4-4	2	2	CARGWMKTGFRGYPSWVYFDLWG	Px4-4	Px4-4	none
4-10	1-18	3	3	CVRDGSIFLNLPSGHDVFDIWG	unique	unique	none
4-6	1-69	4	4	CARGGDYSGWYHFDYWG	Px4-1, Px4-3	Px4-1, Px4-3	none
4-16	1-69	4	4	CARGGDYSGWYHFDYWG	Px4-1, Px4-3	Px4-1, Px4-3	none





Conclusion

- Pemphigus patients do not have an ongoing defect in tolerance to desmoglein
- Pemphigus probably results in a one time "hit" with development of a few non-tolerant B cell clones
- If the oligoclonal B cells can be eliminated, disease can be cured

Acknowledgments

- Aimee Payne
- Ken Ishii
- Jun Yamagami
- Yasushi Hanakawa
- Christoph Hammers
- Chenyan Lin
- Don Siegel
  - Stephen Kacir
- Masayuki Amagai
  - Kazuyuki Tsunoda

CLAYTON E. WHEELER LECTURE

Milestones in Pemphigus and Pemphigoid Pathogenesis

Luis Diaz, MD

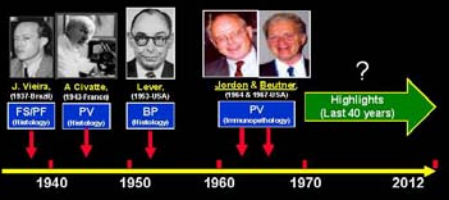
The 36th Annual Southeastern Consortium for Dermatology

Clayton E. Wheeler Lecture

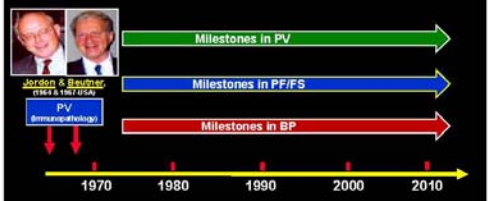
"Milestones in Pemphigus and Pemphigoid"

Luis A. Diaz, M.D.

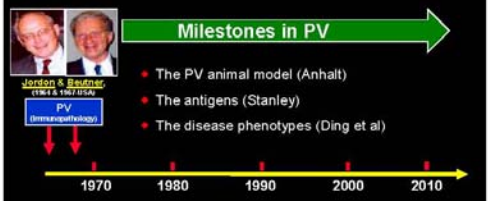
Milestones in Pemphigus and Pemphigoid



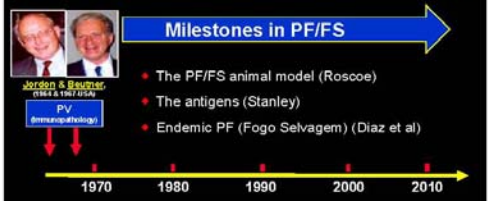
Milestones in Pemphigus and Pemphigoid



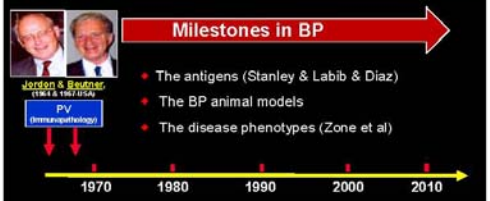
Milestones in Pemphigus and Pemphigoid

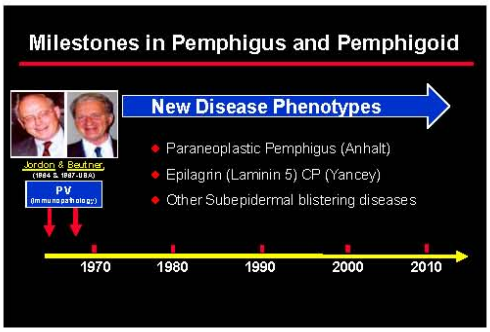


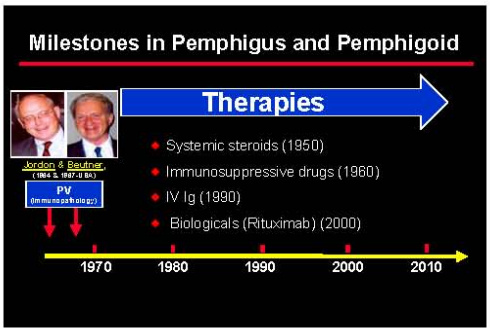
Milestones in Pemphigus and Pemphigoid



Milestones in Pemphigus and Pemphigoid




Milestones in Pemphigus and Pemphigoid
New Disease Phenotypes
Jordon & Beutner
PV
Paraneoplastic Pemphigus (Anhalt)
Epilagrin (Laminin 5) CP (Yancey)
Other Subepidermal blistering diseases
1970
1980
1990
2000
2010


Milestones in Pemphigus and Pemphigoid
Therapies
Jordon & Beutner
PV
Systemic steroids (1950)
Immunosuppressive drugs (1960)
IV Ig (1990)
Biologicals (Rituximab) (2000)
1970
1980
1990
2000
2010

Primary Focal Hyperhidrosis

Alma Cruz, MD

PRIMARY FOCAL HYPERHIDROSIS

Alma M. Cruz, MD

Primary Focal Hyperhidrosis (PFHH)

- Disorder of excessive sweating out of proportion with thermoregulatory requirements
- Bilateral and relatively symmetric
- Most common in : axillae, palms, sole or craneofacial region
- Result in occupational,psychological and physical impairment and social stigmatization

EPIDEMIOLOGY

- 200 millions people worldwide
- 2.8% of the population in USA suffers PFHH
- male = female
- 2/3 not treated
- Distribution of PFHH
  - Axillae-51%
  - Soles-30%
  - Palms-24%
  - Face-10%
- Genetics
  - Strong family history in 30-50%
  - Autosomal dominant with variable penetrance

ANATOMY

- Human skin has ~4 million sweat glands:
  - Apocrine
  - Eccrine
  - Apoeccrine

ANATOMY

- **Eccrine**
  - Odorless, clear, hypotonic solutions (watery secretions)
  - Thermoregulation (regulated by thermal, gustatory and emotional stimuli)
  - Electrolyte balance
  - Sensitive to cholinergic stimulation (Innervated by postganglionic sympathetic cholinergic fibers)
- Involved in HH

ANATOMY

- ANATOMY
  - **Apocrine:**
    - Develop during puberty in conjunction with hair follicles (Groin and axillae)
    - Viscous and cloudy secretions
    - Sensitive to adrenergic stimulation
    - NOT involved in HH
    - Exact function unclear, thought to represent sweat glands

ANATOMY

- ANATOMY
  - **Apoeccrine**
    - Hybrid gland
      - eccrine & apocrine elements
    - Axillae and perianal area
    - Found in patients with axillary HH
    - Secretory rate 7-fold higher than normal eccrine glands
    - Function unknown

PHYSIOLOGY OF SWEAT

- Change in body temp, emotional stimuli, pain or dietary
- Activation of skin receptors
- Afferents fibers pass impulses via Aγ & C to CNS
  - Spinal cord - thermosensitive neurons
  - Brain stem-reticular formation and raphe nucleus
  - Hypothalamus (thermoregulatory control center in the brain)– **pre-optic nucleus and anterior hypothalamus**
- Efferent fibers from hypothalamus
  - Spinal cord
  - Sympathetic Ganglia
  - Postganglionic C fibers innervated sweat glands
    - **release Ach** which binds to postsynaptical M3 muscarinic receptors which **trigger sweat production**

PATHOPHYSIOLOGY OF FHH

- Pathophysiology unknown
- Not associated with other sign or symptoms of autonomic dysfunction
- Normal morphology and histology of eccrine glands
- Apocrine glands in patients with axillary HH exhibit hypertrophy and overactivity compared with those in normal controls

ETIOLOGY OF FHH

- Etiology unknown
- Suspected dysfunction of the sympathetic nervous system
- Can be associated with increase cholinergic stimulation of axillary sweat glands, yet normal catecholamine levels
- Other area in the brain regulate the sweat
  Palmo-plantar sweating controlled by cerebral cortex
  - does not occurs during sleep or sedation
  - direct corticospinal sudomotor pathway
- Axillary sweating controlled by both emotional and thermoregulatory stimuli
- Genetic component- up to 65% of patients

DIAGNOSTIC EVALUATIONS OF PHH

- Criteria for PHH
  - Focal, visible excessive sweating of **at least 6 months** duration without apparent cause and with at least 2 of the following characteristics:
    - bilateral and relatively symmetric sweating
    - frequency of at least 1 episode per wk
    - Impairment of daily activities
    - age at onset < 25ys
    - positive family history
    - cessation of sweating during sleep

Treatments

- Non-invasive
  - Topical antiperspirant and other topical agents
  - Iontophoresis
  - Systemic medications
- Minimal invasive
  - Botulinum toxin injection
- Surgical
  - Local excision, subcutaneous curettage or liposuction of axillary area
  - Endoscopy Thoracic Symmpathectomy

Treatments

- **Topical**
  - **Aluminum and Zirconium salts**
    - Most common - aluminum chloride solution (20-25%)
      - New: Aluminum Zirconium Trichlorohydrex
      - Hydrosal gel - 15%Aluminum Chloride in 2% Salicilic Acid gel
    - Inexpensive, Non-toxic, works better in axillae than palms/sole, good for mild HH or as adjunct therapy
    - Mechanism of action-mechanical obstruction of the eccrine duct or atrophy of the secretory cells
      - M-Cl + moles BASE ⇄ M(BASE) +nHCl
    - Limitations - burning, stinging and irritation

Treatments

- **Astringent Agents**
  - Denatured keratin in the eccrine duct
  - Result in superficial blockage
  - Agent used:
    - Formaldehyde - irritation, dicoloration and contact dermatitis
    - Glutaraldehyde
    - Tannic acid
    - Acetic acid

Treatments

- **Anticholinergic** - Topical glycopyrrolate
  - 0.5-4% cream, aqueous solution or pads
  - Competitive inh. Ach at neuroglandular synapse
  - primarily indicated in craniofacial HH
  - Low efficiency due to poor absorption and cutaneous and systemic side effects

Treatments

- **IONTOPHORESIS**
  - Mechanism of action: Uses electrical current to enhance percutaneous absorption of ions leading to obstruction of distal eccrine ducts or disruption of eccrine gland secretion
  - Procedure: place hands and feet in shallow basin filled with tap water. Apply direct current 10-20mA for 20-30min per session
  - Anticholinergic may be added, increasing efficacy but also adverse events
  - Frequency: qod until euhydrotic ~6-10 sessions
  - FDA approve devices
    - Drionic
    - Fischer MD-1a

Treatments

- **IONTOPHORESIS**
  - Maintenance: every 1-4 weeks
  - Indications: 2nd line of treatment for palmoplantar HH
  - Complication:
    - Time consuming Irritation , dryness, peeling, erythema, vesiculation
  - Contraindicated in pregnant, metal implant in the" current path", cardiac conditions, pacemaker or history of epilepsy

Treatments

- **Botulin Toxin A**
  - Mechanism of action
    - Binds to the presynaptic membrane receptor and Inhibits release of Ach
    - 1 U Botox® = 3-4 U Dysport®

Treatments (Botulin Toxin A)

- Pain Control
  - facial and axilla can be injected without anesthesia
  - Palms and soles
    - topical anesthesia
    - nerve block:
      - medial, ulnal, radial for wrist
      - tibial and sural nerve for ankle
    - Bier's block
    - vibration
    - cold anesthesia

Treatments (Botulin Toxin A)

Dose

- axilla: 2-3 U/1.5-2 cm (50-100 U/axilla)
  - 95% improvement in 1 week
  - lasting 7 mo (4-10 mo)
- palm: 1.5-2.5 U/1-1.5 cm (100-150 U/palm)
  - 90%improvement
  - lasting 4-6 mo
- sole: 1.5-2.5 U/1-1.5cm (150-200 U/sole)
  - lasting 5 mo
- craniofacial: 2U/1.5-2cm (50U)
  - 3 horizontal rows along upper third and 2 cm behind anterior frontal hair line
  - 75% improvement
  - lasting 5-6 mo

Treatments (Botulin Toxin A)

- Gustatory
  6-8 U, lasting 1 to 3 years
- Upper lip, Nose
  6-10 U, lasting 4-6months
- Groin
  50-100 U lasting 6 months
- Compensatory HH areas
  100-300 U

Treatments (Botulin Toxin A)

- Adverse Events:
  - compensatory increases in sweating
  - pain
  - mild numbness
  - paresthesia
  - hematoma at the injection site
  - transient weakness of the intrinsic muscle of the area
    - hand begins 1-3 days
    - lasts 10-14 days
    - seen in 45-77% of cases

Treatments (Botulin Toxin A)

- Contraindications
  - Absolute
    - allergy to drug component
    - infection at injection site
  - Relative
    - neuromuscular disorder (myasthenia gravis)
    - pregnancy or lactation
    - age > 65 yrs
    - organic causes of HH
    - medications that interfere with neuromuscular transmission
    - unrealistic expectation or psychiatric illness such as dysmorphic disorder

Treatments

- **Local Surgery**
  - Limited to axillary HH
  - Small series reported
  - **Curettage / Liposuction**
    - The more aggressive the more effective
    - but more side effect: paresthesia, scar, hematoma, skin erosion
  - **Excision**
    - Entire axilla- limitation in the range of motion
    - Modified excision - 65%

Treatments

- **Laser Devices**
  - All are off- label
  - Nd-Yag 1064 subdermal apply 10 to 20 J per axilla

Emerging New Therapies

- **Microwave technology**
  - miraDry System
  - FDA cleared Jan/2011- Commercially available since Oct/2011
  - For axillary HH
  - Used microwave energy, resulting in thermolysis of the sweat glands causing long term permanent destruction of the glands
  - 1hour per underarm

Emerging New Therapies

- **Ultrasound Therapy - VASER**
- 3th generation FDA cleared for fat emulsification/aspiration & body contouring
- Deliver ultrasonic energy at the tip of a probe
- For axillary HH
- Required local +/- IV sedation

Emerging New Therapies

- **New Topical Option-(Hydrosal ®)**
- 15% Aluminum Chloride in 2% salicylic acid
- For axillary HH
- Aplly every night
- Most imp low degree of irritation compare with Dry-Sol
- Over the counter

ORAL AGENTS

- Anticholinergics - (glycopyrrolate) Robinul
  - Competitively inhibit Ach at the neuroglandular synapses
  - 1mg - 2mg tablets
  - Start 1mg po bid
  - Increase 1mg q 2 weeks depending on clinical effect and tolerability

ORAL AGENTS

- Anticholergics (cont'd)
  - adverse events
    - dry mouth
    - reduced gastric secretion
    - blurred vision, mydriasis
    - urinary retention, slowed voiding
    - tachycardia

WHO DO I TREAT WITH ORAL ANTICHOLINERGIC?

Possible pts	Not good candidates
Multiple areas of involvement	Athletes
Generalized HH	School sports
Craniofacial	Construction & outdoors workers
Failed other first line of tx	Children

ANTICHOLINERGICS

- Contraindications
  - glaucoma
  - impaired gastric emptying
  - hx of urinary retention

ORAL AGENTS

- Benzodiazepine
  - Controlled substance
  - Treatment of anxiety and alcohol withdrawal
  - Act on the CNS: limbic, thalamic and hypothalamic regions
  - Anxiety-induced HH

ORAL AGENTS

- Beta Blocker: Propanolol
  - 5-10mg
  - patient with known anxiety-evoked sweating
    - giving presentation, job interview
  - take 30-60 min before event

ORAL AGENTS

- Others
  - Clonidine
  - Ca^{++} chanel blockers
  - Indomethacin
  - Anticonvulsant - gabapentin

SURGICAL PROCEDURES

- Endoscopic Thoracic Sympathectomy
  - Sympathectomy start 1889 and re-emerge 1980
  - Short time F/U
  - Lack of consistency in surgical method
  - Lack of large randomized, prospective clinical trials
  - Many are retrospective data analysis

SURGICAL PROCEDURES

- Endoscopic Thoracic Sympathectomy
  - destroy by resection, ablation or clipping bilateral thoracic ganglia through endoscopy technique
  - Palmar HH (T3 and T3-T4)
    - 95% cure
    - Recurrent sweating (7-39%)
    - Satisfaction declines with time (66-93%)
  - Axillary HH ((T4 or T3-T4)
    - 67% up to 65% improvement
    - Recurrent sweating 15-35%
    - Satisfaction 66%

SURGICAL PROCEDURES

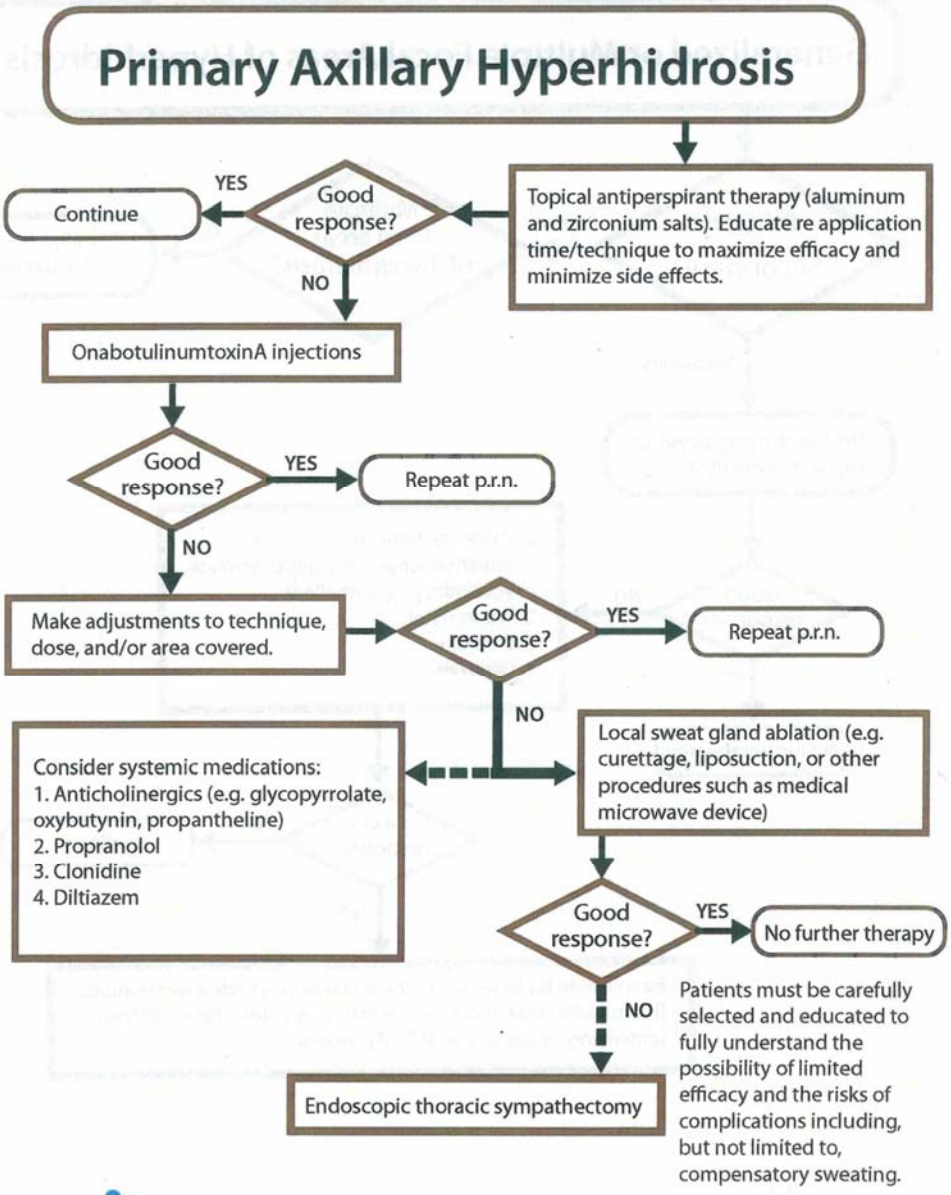
- Endoscopic Thoracic Sympathectomy
  - Craniofacial HH (T3 and T3-T4)
    - 1314 treated
    - Of the 831 responder 85% were satisfied
    - 83% reported CS (trunk)
  - Plantar HH
    - Endoscopic Lumbar Sympathectomy
    - Cured HH in 97% (new technique ,minimal data)
    - CS in 44% and sexual dysfunction (8- 54%)

SURGICAL PROCEDURES

- Complications of ETS
  - COMPENSATORY SWEATING >50%
  - excissively dry hands, gustatory sweating,
  - Horner Syndrome, phantom sweating, neuropathies
  - sexual dysfunction (plantar)
  - perioperative complications
    - pneumothorax (intercostals 4-5)
    - Cardiac arrest, etc.

Thank You

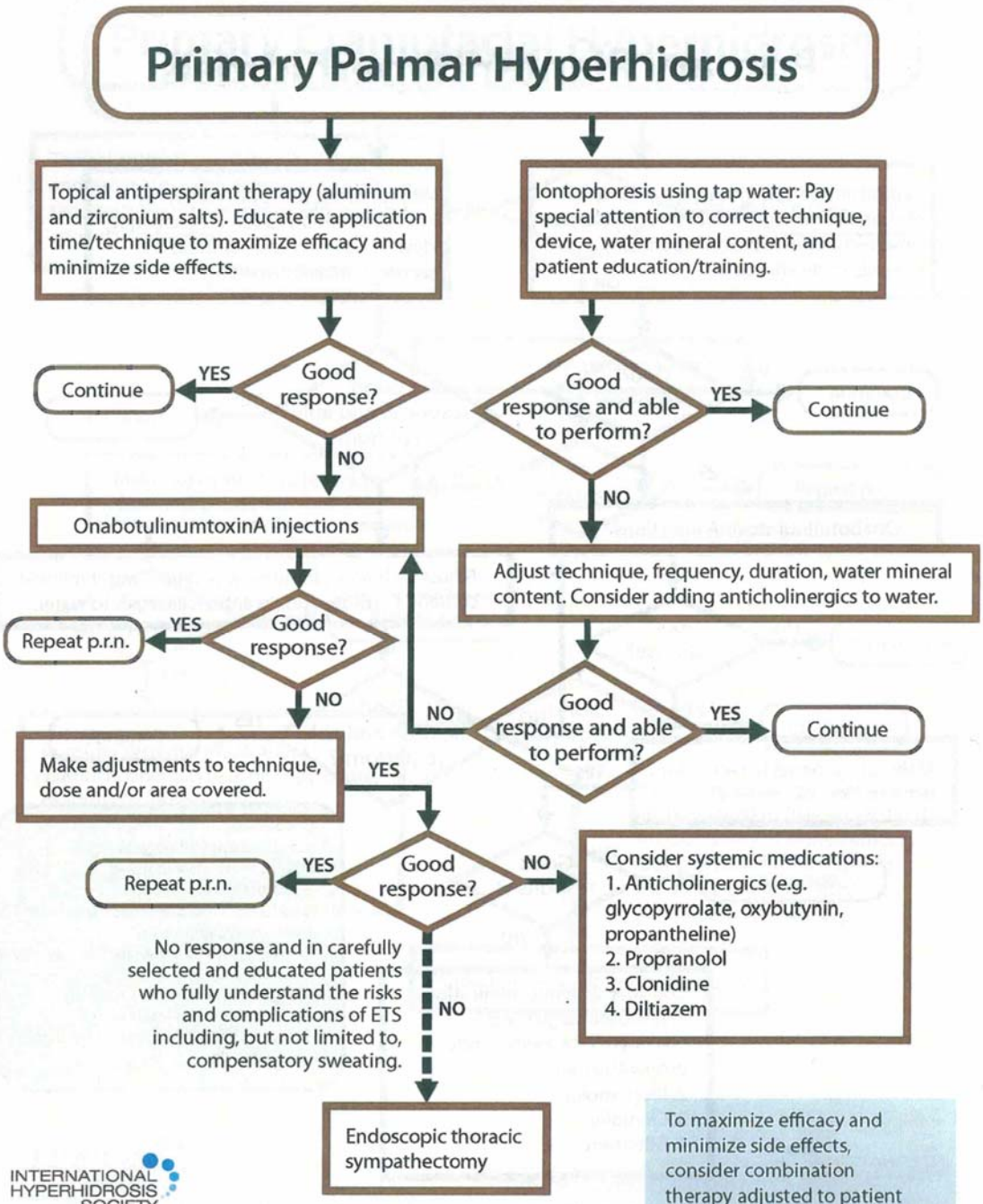
Primary Axillary Hyperhidrosis



INTERNATIONAL HYPERHIDROSIS SOCIETY
Know Sweat
www.SweatHelp.org

Updated: June 8, 2012

To maximize efficacy and minimize side effects, consider combination therapy adjusted to patient needs and disease presentation.



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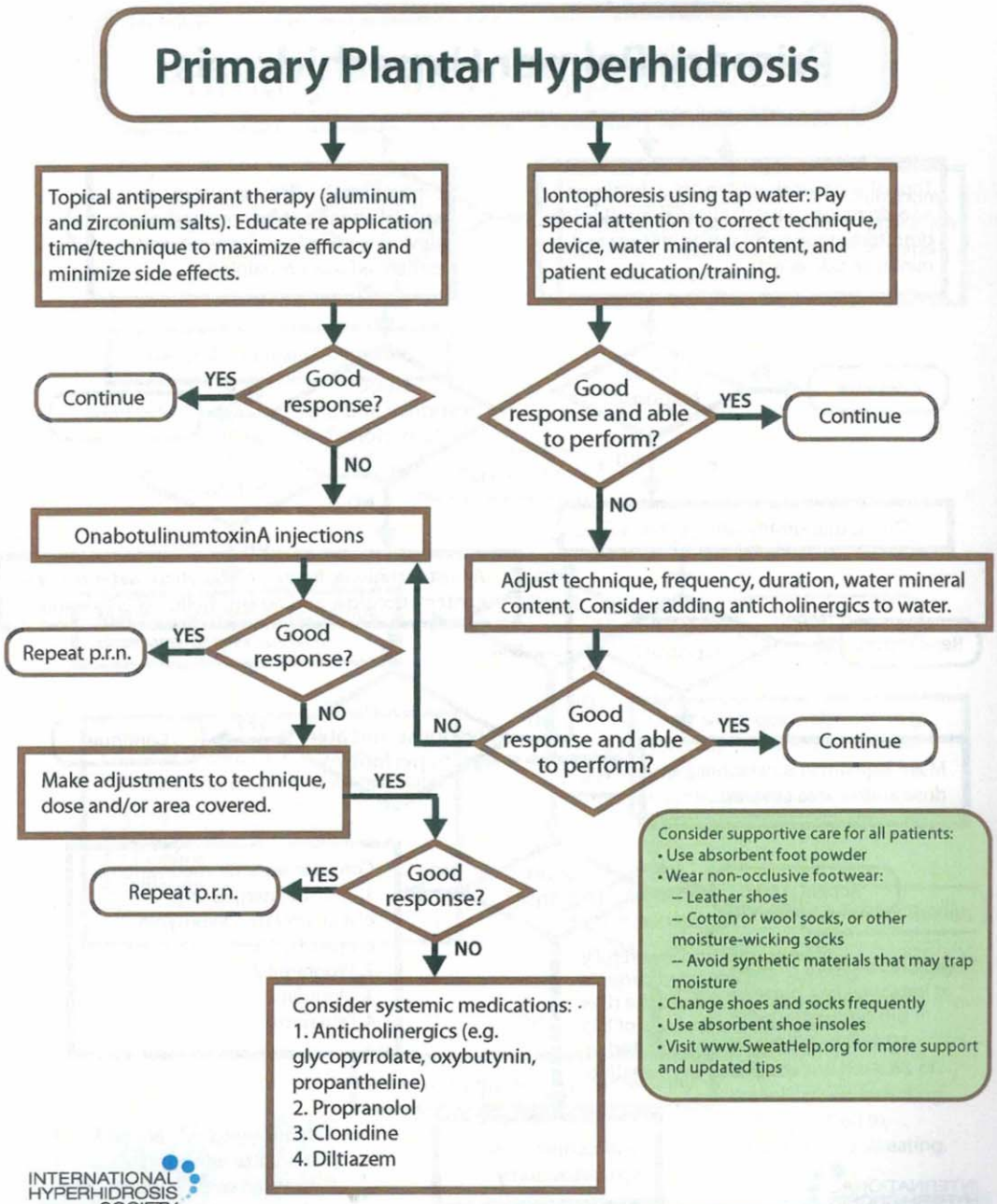
Updated: January 15, 2012


Primary Plantar Hyperhidrosis
Topical antiperspirant therapy (aluminum and zirconium salts). Educate re application time/technique to maximize efficacy and minimize side effects.
Iontophoresis using tap water: Pay special attention to correct technique, device, water mineral content, and patient education/training.
Good response?
YES
Continue
NO
Good response and able to perform?
YES
Continue
NO
OnabotulinumtoxinA injections
Adjust technique, frequency, duration, water mineral content. Consider adding anticholinergics to water.
Good response?
YES
Repeat p.r.n.
NO
Good response and able to perform?
NO
YES
Continue
Make adjustments to technique, dose and/or area covered.
YES
Good response?
YES
Repeat p.r.n.
NO
Consider systemic medications:
1. Anticholinergics (e.g. glycopyrrolate, oxybutynin, propantheline)
2. Propranolol
3. Clonidine
4. Diltiazem
Consider supportive care for all patients:
• Use absorbent foot powder
• Wear non-occlusive footwear:
-- Leather shoes
-- Cotton or wool socks, or other moisture-wicking socks
-- Avoid synthetic materials that may trap moisture
• Change shoes and socks frequently
• Use absorbent shoe insoles
• Visit www.SweatHelp.org for more support and updated tips
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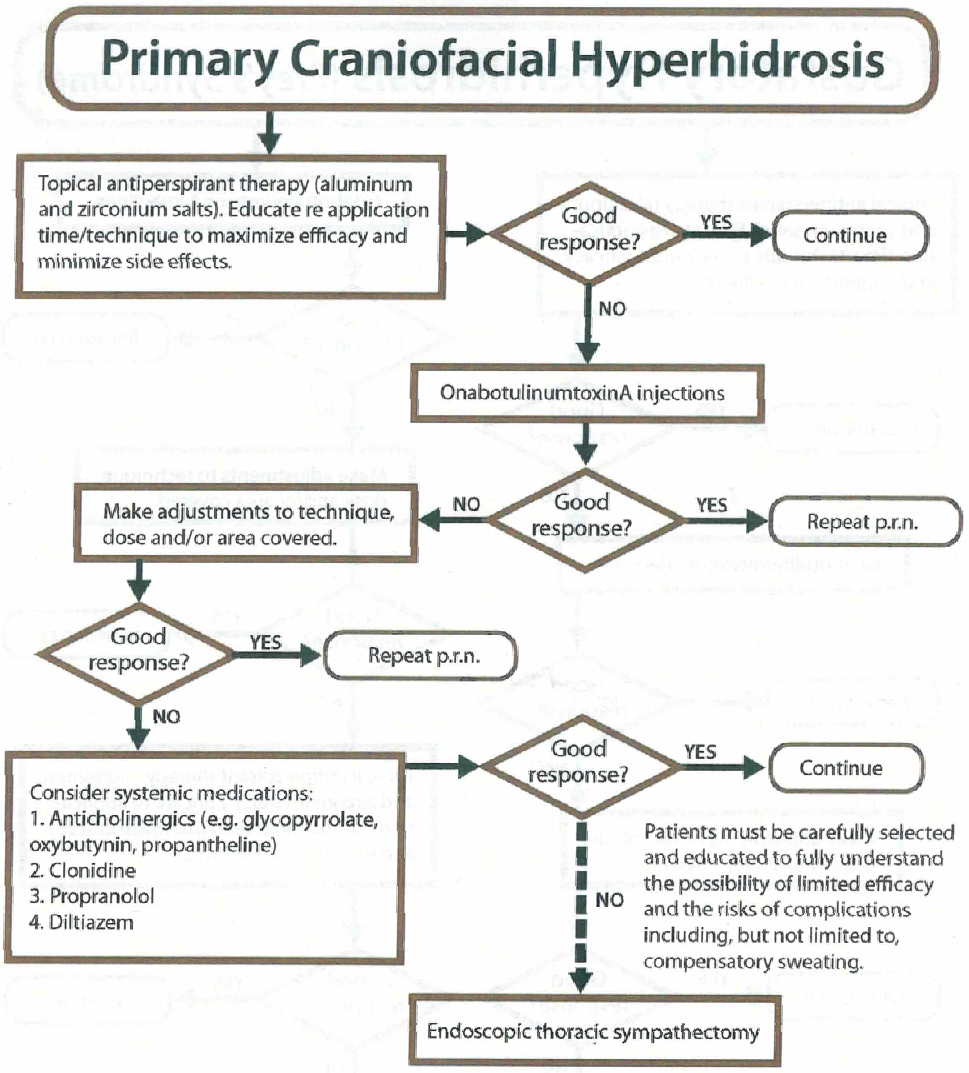
To maximize efficacy and minimize side effects, consider combination therapy adjusted to patient needs and disease presentation.

Primary Craniofacial Hyperhidrosis



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To maximize efficacy and minimize side effects, consider combination therapy adjusted to patient needs and disease presentation.

Urticaria, Angioedema, and Delayed Pressure Urticaria

Thomas Cropley, MD

Therapeutic Dilemmas: Urticaria, Angioedema, and Delayed Pressure Urticaria

Thomas G. Cropley, M.D.
University of Virginia

- I have no industry relationships or other conflicts of interest to disclose.
- I will discuss off-label use of medications in this talk (indicated▲)

Topics to be covered

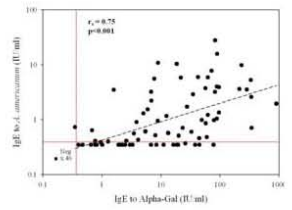
- Acute and episodic urticaria
- Chronic urticaria
- Angioedema
- Delayed pressure urticaria

First, a local story…

- 2005 - 2007: 20% of pts in TN, AR, VA, NC, MO treated with **cetuximab**, a monoclonal anti-EGFR antibody for cancer, experience anaphylaxis.
- Pts in other regions of U.S. do not
- Affected pts are found (UNC, Vanderbilt) to have preexisting IgE antibodies to an oligosaccharide on the Fab portion of the mAb, called *galactose-alpha-1,3-galactose* (a.k.a., *alpha-gal*)
- For the most part, only pts is Southeastern U.S. have the antibodies

- 2009 - 2011: clinical queries and screening of sera from several thousand patients (UVa and UNC) from S.E. region shows that pts with IgE to *alpha-gal* frequently report generalized urticaria or anaphylaxis after eating red meat.
- Some note onset of meat allergy after multiple tick bites.
- *Alpha-gal* is a blood group antigen found in mammals (i.e., red meat) but not fish or poultry

- The geographic distribution in the Southeast corresponds to the expanding range of the Lone Star tick, *Amblyoma americanum*
- Eventually, a strong epidemiologic and immunologic link between *Amblyoma americanum* bites, red meat allergy and *alpha-gal* IgE antibodies is confirmed



Commins S, et al. *J Allergy Clin Immunol* 127: 1286-93, 2011 May.

Definitions

- **Acute urticaria**: Symptoms less than 6 weeks
- **Episodic urticaria:** Symptoms less than twice a week, for longer than 6 weeks (in practice, treated as acute urticaria)
- **Chronic urticaria:** Symptoms occuring at least twice a week, for at least 6 weeks

Acute Urticaria: Etiology

40% viral upper respiratory tract infections
9% drugs
1% foods
50% idiopathic

Zuberbier T, et al. Acta Dermatol Venereol (Stockh), 76:295-7, 1996.

Acute Urticaria: How I Treat

- Avoid aspirin and NSAIDs, opioids
- Discontinue high-probability drugs (e.g., newly started meds)
- Topical antipruritics
- If associated angioedema, Rx **epinephrine autoinjector** *and teach its correct use*

Acute Urticaria: How I Treat

- Nonsedating **H1** blocker at conventional dose (e.g., **cetirizine** or **loratadine** 10mg q24hr, or **fexophenadine SR** 180mg q24hr)
- Sedating H1 blocker for breakthrough (e.g., **hydroxyzine** 10 – 30mg q6-8hr prn or **diphenhydramine** 25-50mg q6-8hr prn)
- IF NOT CONTROLLED AFTER 48 - 72 HOURS →

Acute Urticaria: How I Treat

- ▲ Double nonsedating **H1** blocker (e.g., **cetirizine** or **loratadine** 10mg q12hr, or **fexophenadine SR** 180mg q12hr)
- IF NOT CONTROLLED AFTER 48 - 72 HOURS →

Acute Urticaria: How I Treat

- ▲ Add H2 blocker (e.g., **ranitidine** 150mg q12hr, or **cimetidine** 400mg q8hr)
- IF NOT CONTROLLED AFTER 48 - 72 HOURS →

Acute Urticaria: How I Treat

- **Prednisone** 1mg/kg/24hr up to 60mg/24hr. Taper over 2-3 weeks.
- May opt to start prednisone sooner
- Decision to use prednisone is based on severity of symptoms (e.g., associated angioedema, sleep deprivation)
- IF NOT CONTROLLED AFTER 48 - 72 HOURS →

Acute Urticaria: How I Treat

- Change to different nonsedating and sedating H1 blockers
- Consider adding ▲ **doxepin** in place of sedating **H1** blocker (especially useful if severe sleep disturbance)

Evidence-Based Reality Check

- Evidence for **H2** blockers is poor (4 old RCTs, "high risk of bias")
  Cochrane Database Syst Rev 2012 Mar 14;3:CD008596.
- Evidence for updosing nonsedating **H1** blockers is just as poor (most studies show no significant difference in low- and high-dose groups, just trend toward better response at higher doses) J Invest Allergol Clin Immunol 2011;21 Suppl 3:34-9.

Episodic Urticaria

- Much more likely than single-episode acute urticaria or chronic urticaria to be due to allergy (food, drug)
- Anaphylaxis risk is higher
- Food allergy testing has fairly high yield
- Pharmacologic treatment: same as single-episode acute urticaria, but avoid long-term prednisone

Chronic Urticaria

35% physical urticarias
5% urticarial vasculitis
5% infection (*Strongyloides*, ? *H pylori*)
5% "pseudoallergy": induction of leukotrienes by drugs; e.g., aspirin and NSAIDs
25% idiopathic
25% autoimmune (anti-IgE Fab antibodies vs. non-autoantibody mechanisms)

Chronic Urticaria

35% physical urticarias
5% urticarial vasculitis
5% infection (*Strongyloides*, ? *H pylori*)
5% "pseudoallergy": induction of leukotrienes by drugs; e.g., aspirin and NSAIDs
25% idiopathic
25% autoimmune (anti-IgE Fab antibodies vs. non-autoantibody mechanisms)

When is it Autoimmune?

- **When you think it might be:** otherwise idiopathic; responds to prednisone
- Other associated autoimmune disease (autoimmune thyroid dz; vitiligo; IDDM)
- If circulating anti-IgE Fab antibodies (may or may not be functional); found in 40%
- Positive basophil / mast cell histamine release assay (rarely done in U.S.)
- Positive autologous serum skin test (rarely done)

Chronic Urticaria

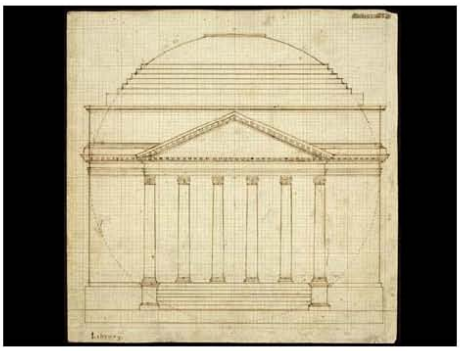
- Treatment of mild chronic urticaria is the same as acute urticaria: H1 and H2 antihistamines, short-term prednisone when required
- ▲ Consider trial of leukotriene antagonist (e.g., **montelukast** 10mg/24hr)

Chronic Urticaria

- **Immunosuppressives** for suspected / possible autoimmune urticaria, especially severe, continuous cases
- My usual: ▲ **azathioprine** 25 – 150mg/day (generally well-tolerated; affects antibody production as well as T cells)
- Other options:
  - ▲ **mycophenolate mofetil** 1500mg - 3000mg/24hr;
  - ▲ **cyclosporine** 3 -5mg/kg/24hr (best evidence: 2RCTs)

When / How to Stop Treatment

- Acute, single-episode: after 7 symptom-free days. Wean prednisone; no wean for antihistamines
- Episodic urticaria and chronic urticaria: after symptom-free for 6-8 weeks. Wean prednisone and immunosuppressives; no wean for antihistamines



Angioedema with Wheals

- Is **never** due to hereditary or acquired C1 inh deficiency
- Manage as for urticaria (acute, episodic, or chronic)
- Risk of airway compromise: Rx **epinephrine autoinjector**

Angioedema without Wheals

- **If C4 is low:** C1 inh deficiency (hereditary or acquired). Further w/u to define which. Treat with **C1 inh concentrate** or **FFP** for emergencies and elective surgery; **danazol** for maintenance.
- **If C4 normal:** Drugs (e.g., Type 1 ACEi's); idiopathic, rarely other syndromes: treat as for urticaria after d/c drugs such as ACEi's

Delayed Pressure Urticaria

- Easy to diagnose if you think of it!
- Patient may not recognize relation to pressure stimulus due to time lag
- Resembles angioedema but painful / tender
- Usually associated with ordinary spontaneous urticaria as well as dermographism

Delayed Pressure Urticaria

- **Prednisone** (short term; e.g., prophylaxis before dental procedures, long plane flights)
- ▲ **Sulfasalazine** 2-4gm/24hr (check G-6PD)
- ▲ **Dapsone** 50 – 150mg/24hr (check g-6PD)
- ▲ **Montelukast** 10mg/24hr

My Approach to Hand Eczema

Aída Lugo-Somolinos, MD

MY APPROACH TO HAND DERMATITIS

Aida Lugo-Somolinos MD

"Dermatitis" Defined

Suzanne M. Smith and Susan T. Nedorost

Dermatitis, Vol 21, No 5 (September/October), 2010: pp 248-250

1. Dermatitis is any inflammation of the skin.		
	Response Percent	Response Count
True	50.0%	61
False	50.0%	61

2. I use the term 'dermatitis' as interchangeable with the term 'eczema.'		
	Response Percent	Response Count
True	47.6%	58
False	52.5%	64

"Dermatitis" Defined

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Conclusion

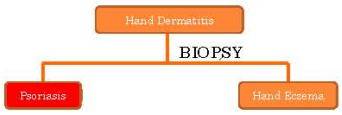
There is a lack of consensus among experts as to the definitions of the terms "dermatitis" and "eczema."

ECZEMA

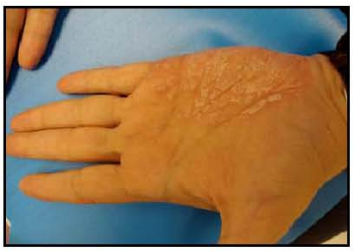
- Type of inflammatory reaction of the skin characterized by erythema, edema, papules, and crusting with or without vesicles; finally followed by lichenification and scaling of the skin. Variable degrees of itching.

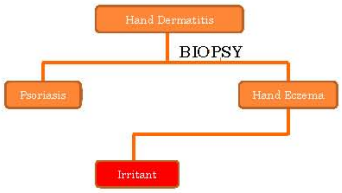
- There is no generally accepted classification of hand eczema.
- A 3-step classification is proposed:
  - A) An etiological diagnosis where possible
  - B) A diagnosis based on the morphology of the dermatitis.
  - C) Identification of the dynamics of the dermatitis.

- The most common etiological groups seen in Meding and Swanbeck's study (2003) were:
  - Irritant contact dermatitis (35%)
  - Atopic dermatitis (22%)
  - Allergic contact dermatitis (19%)
  - Unclassified eczema (15%)
  - Few had nummular hand eczema, hyperkeratotic hand eczema, or pompholyx.



PSORIASIS





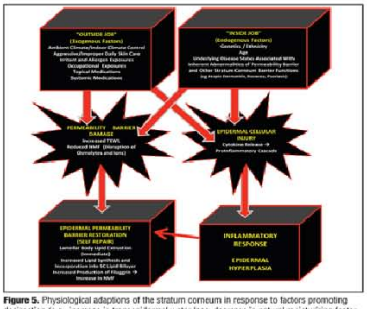


Figure 5. Physiological adaptions of the stratum corneum in response to factors promoting desiccation (e.g., increase in transepidermal water loss, decrease in natural moisturizing factor, damage or reduction in stratum corneum lipids, damage to stratum corneum proteins)

IRRITANT

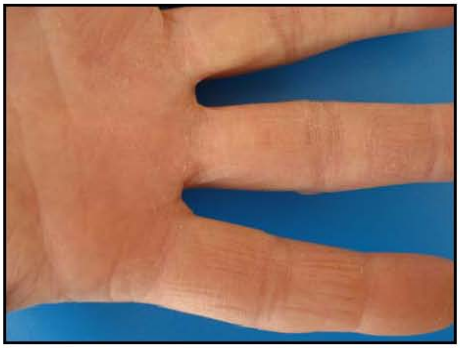
- Most frequent form 35% HD (60% OHD)
- Occupations at risk- food handlers, housekeepers, health care, mechanics

TOP IRRITANTS

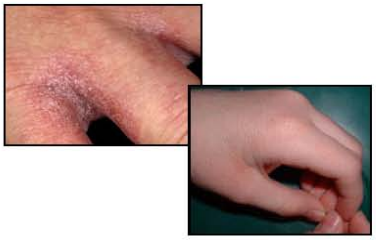
CLINICAL

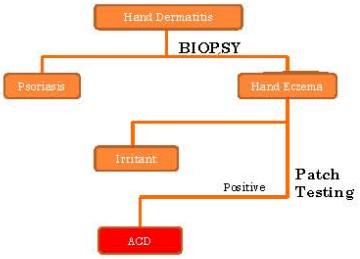
- Rietschel and Fowler proposed the following as primary diagnostic criteria for irritant contact dermatitis:
  - Macular erythema, hyperkeratosis, or fissuring predominating over vesiculation
  - Glazed, parched, or scalded appearance of the epidermis
  - Healing process beginning promptly on withdrawal of exposure to the offending agent
  - Negative results on patch testing that includes all possible allergens

- Minor objective criteria for irritant contact dermatitis:
  - Sharp circumscription of the dermatitis
  - Lower tendency for the dermatitis to spread than in cases of allergic contact dermatitis



IRRITANT DERMATITIS



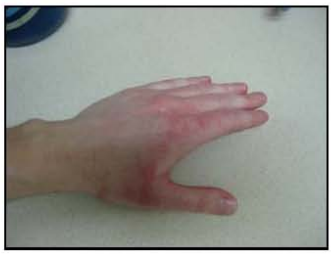


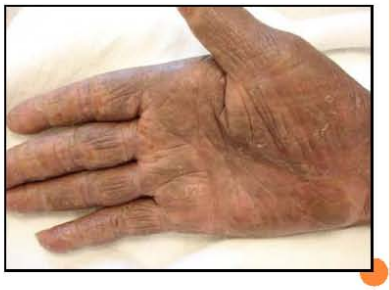
- TRUE test has 35 allergens and control
- Misses up up to 40% relevant allergens
- May be a good screening test
- NA-65
- Special trays
- Expert reader

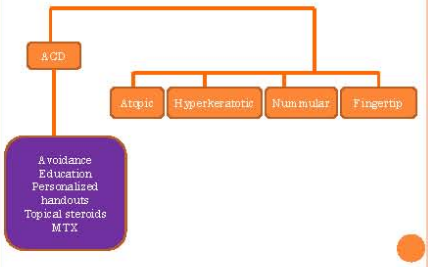
ALLERGIC CONTACT

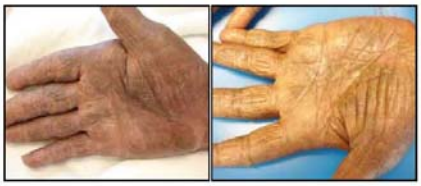
- 19% of hand eczema
- Favors
  - Thinner dorsal skin > acral skin
  - Fingertips> palms

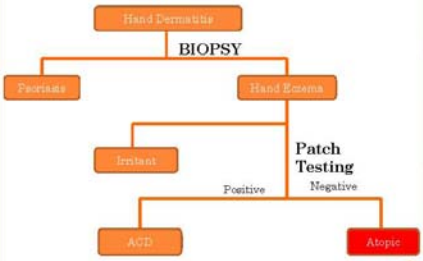
ALLERGIC CONTACT DERMATITIS





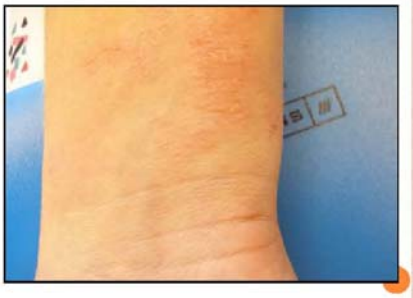


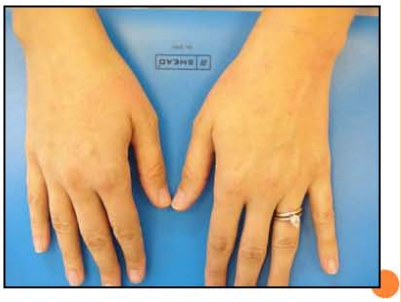


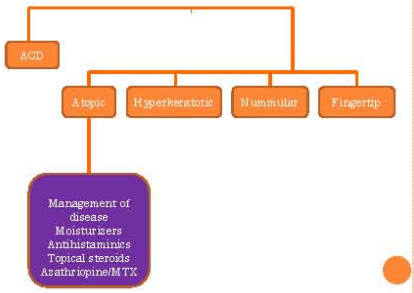


ATOPIC

- 22% of hand dermatitis
- Clinical clues
  - Volar wrists
  - Fingertips
  - Dorsal hands



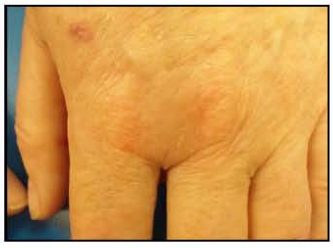


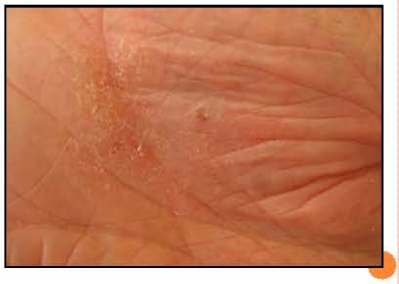


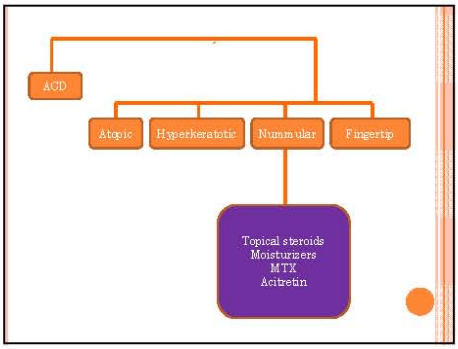
NUMMULAR

- Coined-shaped dermatitis
- Distal fingers and dorsal hands
- Asymmetrical
- May be assoc to + patch tests

NUMMULAR ECZEMA



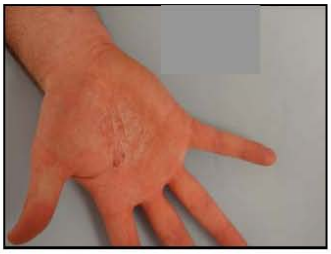


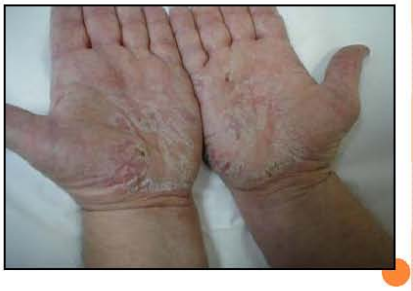


HYPERKERATOTIC

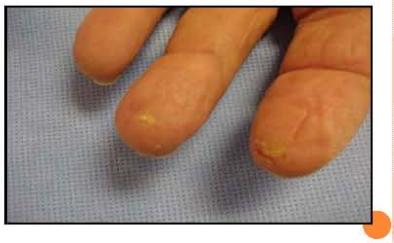
- 2% OF HAND DERMATITIS
- Psoriasiform plaques
- Painful fissures
- 40-60 years old males
- 1/3 have hx of manual labor
- Absence of nail/arthritis
- Very refractory to treatment

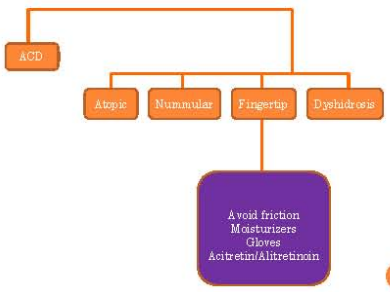
HYPERKERATOTIC

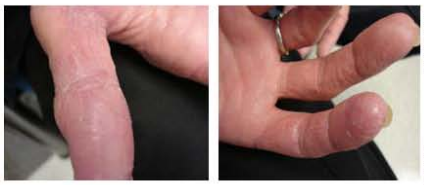


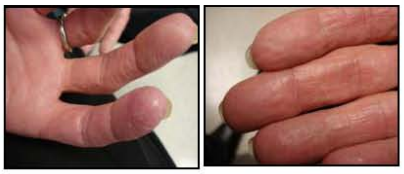


FINGERTIP DERMATITIS









S/P 8WEEKS ACITRETIN

OTHER

- Phototherapy
- Cyclosporine
- Tacrolimus/ pimecrolimus
- Iontophoresis
- Botox

HERBERT Z. LUND LECTURE

Lessons From Pemphigus Research on How to be a Physician Scientist

John Stanley, MD

Herbert Z. Lund Lecture

Lessons from pemphigus research on how to be a physician scientist

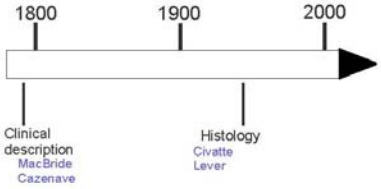
An egocentric historical summary

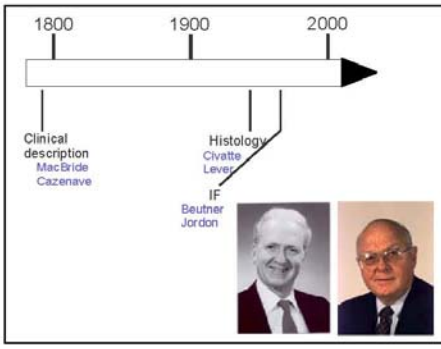
Lesson 1: for best success in research be young!

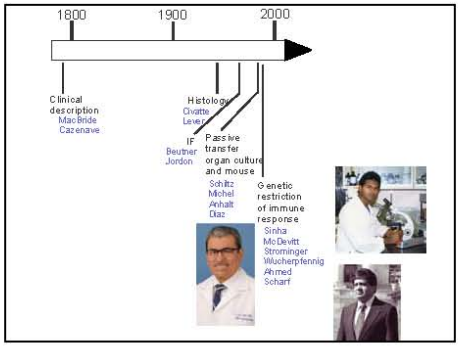
Lesson 2: before starting research--get good armor or find a good mentor (or both)

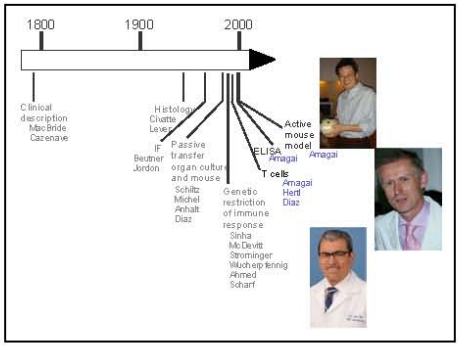
Lesson 3: be obsessed

Lesson 4: stand on the shoulders of others






1800
1900
2000
Clinical description
MacBride
Cazenave
Histology
Civatte
Levers
IF
Beutner
Jordon
Passive transfer organ culture and mouse
Schiltz
Michel
Anhalt
Diaz
Genetic restriction of immune response
Sinha
McDevitt
Strominger
Wucherpfennig
Ahmed
Scharf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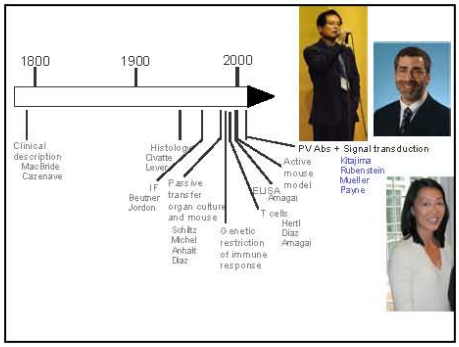
Scharf
Active mouse model
Amagai
ELISA
Amagai
T cells
Amagai
Hertl
Diaz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Genetic restriction of immune response
PV Abs + Signal transduction
Kitajima
Rubenstein
Mueller
Payne
Active mouse model
ELISA
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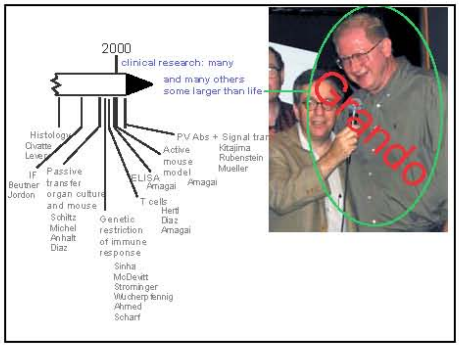
T cells
Hertl
Diaz
Amagai


2000
clinical research: many
and many others
some larger than life
Histology
Civatte
Levers
IF
Beutner
Jordon
Passive transfer organ culture and mouse
Schiltz
Michel
Anhalt
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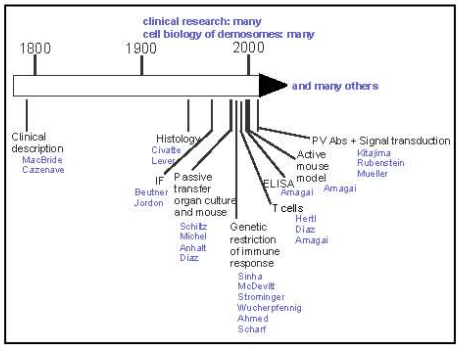
clinical research: many
cell biology of demosomes: many
1800
1900
2000
and many others
Clinical description
MacBride
Cazenave
Histology
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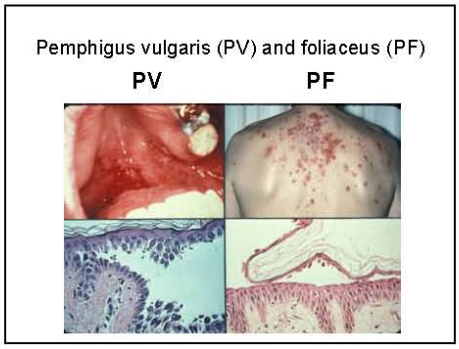
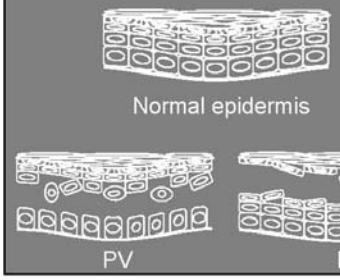
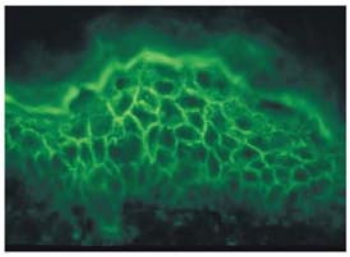

Pemphigus vulgaris (PV) and foliaceus (PF)
PV
PF

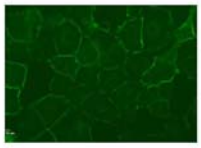
Lesson 5: think simplistically

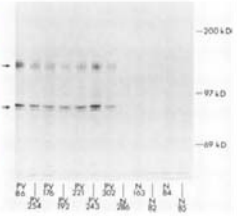


Pemphigus anti-epidermal autoantibodies are found in skin and serum of patients



Immunoprecipitation of PV antigen from keratinocyte culture

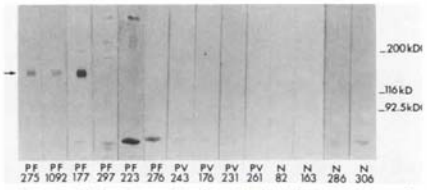




Lesson 6: see it first

PVAg is 130-kd linked to 80 kd
Stanley,Koulu, Thivolet **J Clin Invest** 1984

Immunoblot: PFAg is 160-kD, conformation important for PF ab binding

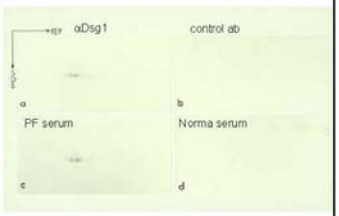


Lesson 7: the best scientists think of the most controls

Stanley,Koulu, Thivolet **J Clin Invest** 1984

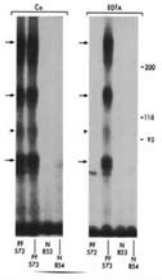
PFAg is desmoglein 1 (Dsg1): first autoimmune disease targeting desmosome

2-D immunoblot of epidermal extract



Koulu, Kusumi, Steinberg, Klaus-Kovtun,Stanley, **JExpMed** 1984
Stanley,Koulu,Klaus-Kovtun,Steinberg **J Immunol** 1986

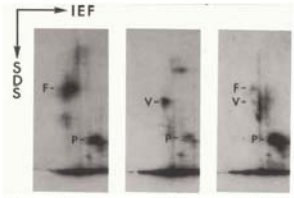
PF Abs bind calcium-sensitive epitopes



Lesson 8: listen to your postdoctoral fellows

Eyre, Stanley, **JExpMe**d 1987

PF and PV Ags complex with plakoglobin

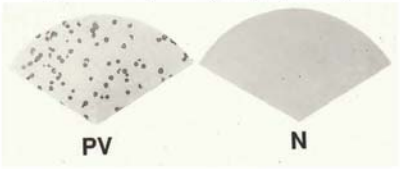


IP with: PF PV αPlak

Korman,Eyre,Klaus-Kovtun,Stanley, **New Engl J Med** 1989

Molecular cloning indicates PV antigen is a previously unknown desmoglein

λgt11 clone expressing pemphigus antigen



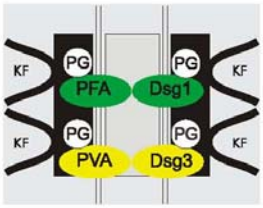
Lesson 8 (again): listen to your postdoctoral fellows

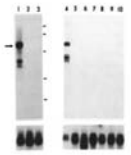
Amagai,Klaus-Kovtun, Stanley, **Cell** 1991

Lesson 9: science is amazing, fun, beautiful and exciting: enjoy it

1991: PV and PF, disorders of cell adhesion, are the first autoimmune diseases of the desmosome

PV and PF: related but distinct disorders of adhesion have related but distinct autoantigens in the desmosome, an adhesion structure



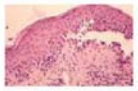


Lesson 10: do not let the senior investigator do any of your experiments

Northern blots: Amagai, Stanley, Cell 1991

very poor loading control; only this part of Northern done by John Stanley!

IP defines a new disease: paraneoplastic pemphigus

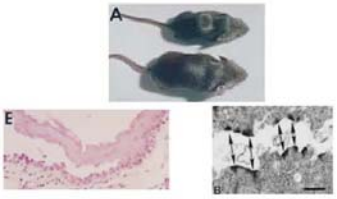


Lesson 11: collaborate

Anhalt,Kim,Stanley,Korman, Jabs,Kory,Izumi,Ratnelli,Mustasim, Ariss-Abso,Labib, **New Engl J Med** 1990

Knockout mouse: loss of desmoglein 3 results in PV

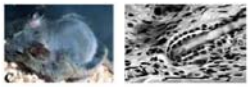
Lesson 12: embrace new technology



Koch,Mahoney,Ishikawa,Pulkinin,Uitto,Shultz,Murphy,Whitaker-Menezes,Stanley, **J Cell Biol** 1997

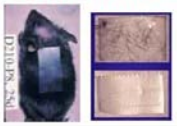
Dsg3 anchors telogen hair

Dsg3-/-



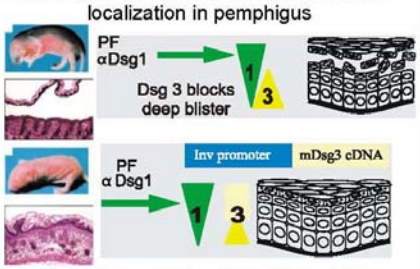
Lesson 12 (again): be creative, devise new technology

The Scotch Tape Hair Test!



Koch,Mahoney, Cotsarelis, Rothenberg,Lavker, Stanley, **J Cell Sci** 1998

Desmoglein compensation explains blister localization in pemphigus



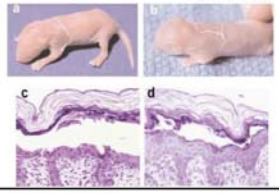
Mahoney, Wang,Rothenberger,Koch,Amagai,Stanley, **J Clin Invest** 1999
Wu,Wang,Yan,Lyle,Fakharzadeh,Wahl,Wheelock, Ishikawa,Uitto,Amagai,Stanley **New Engl J Med** 2000

PF and bullous impetigo share common pathophysiology

Lesson 13: do not think too linearly; think about several things at once

PF

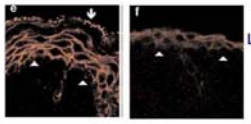
Staph exfoliative toxin (ETA)



Staph exfoliative toxin cleaves Dsg1

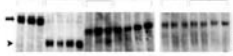
IIF for Dsg1

mouse injected with: buffer exfoliative toxin



Lesson 6 (again) see it first

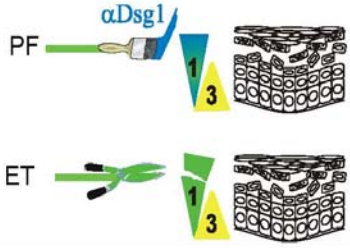
mice injected with: PBS ETA PBS ETA PBS ETA



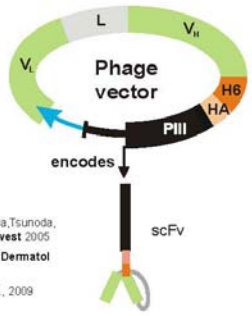
IB with anti-: Dsg1 Blot Dsg3

Amagai,Matsuyoshi, Wang,Stanley, **Nat Med** 2000

Lesson 9 (again): science is beautiful and exciting



Phage display cloning of mAbs from a pemphigus patient

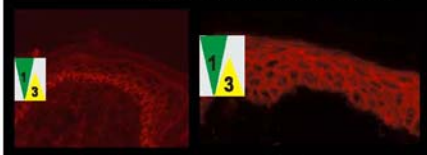


Payne,Ishii,kacir,Lin,Li,Hanakawa,Tsunoda, Amagai,Stanley,Siegel **J Clin Invest** 2005

Ishii,Lin,Siegel,Stanley **J Invest Dermatol** 2008

Yamagami, Stanley **J. Immunol**., 2009

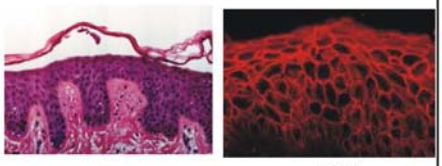
IIF on normal human skin of anti-desmoglein antibodies cloned from a pemphigus patient



αDsg3 scFv

αDsg3/1 scFv

αDsg1 scFv from a PF patient is pathogenic



anti-HA

Use of VH genes in pathogenic and non-pathogenic pemphigus mAbs

Pathogenic:

- PV
  - VH1-69*
  - VH3-07
  - VH1-46
  - VH1-69
  - VH1-46
  - VH1-46
  - VH4b
- PF
  - VH3-30
  - VH3-53

Non-pathogenic:

- PV
  - VH4-04
  - VH1-e
  - VH1-69*
  - VH3-08
  - VH1-46
  - VH5-51
  - VH1-69*
  - VH1-69
  - VH5a
- PF
  - VH1-18
  - VH1-08
  - VH3-09
  - VH3-07
  - VH4-4
  - VH3-30
  - VH3-66
  - VH1-08
  - VH3-09

*originally VH1-4M28, same as VH1-69

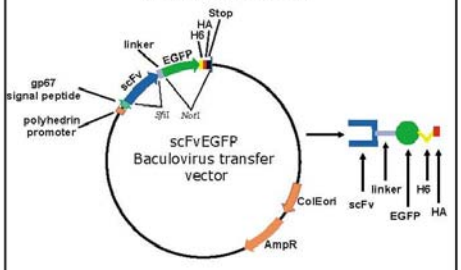
Most pathogenic PV and PF mAbs share a CDR3 consensus amino acid sequence: D/E-x-x-x-W

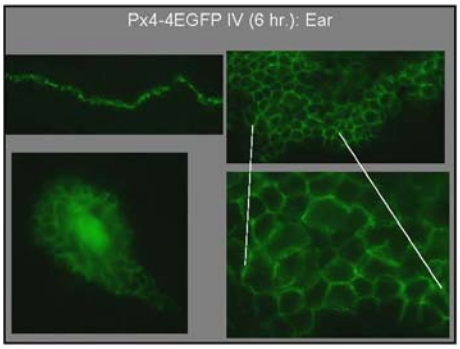
PV1	VH3-07	YYCAS-----GGVVDFDHWGQ
PV1	VH1-46	YYCARD----RQGFDLDVWGQ
PV3	VH1-46	YYCARD----LGGFDFDYWGQ
PF2	VH3-53	YYCVR----GPAYYDIDYWGQ
PV1	VH1-4M28	YYCAR-------GGDYSGWYNFDYWGQ
PF1	VH3-30.3	YYCAR------DRVEGYVWGGTFDHWGQ

Therapy targeted to common sequences of pathogenic autoantibodies may be possible

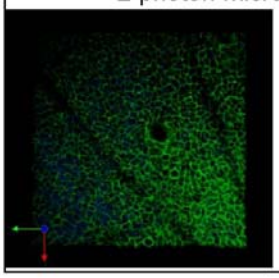
Payne, Siegel, Stanley **J Invest Dermatol 2007**

Non-pathogenic αDsg scFv may be useful for targeted drug delivery



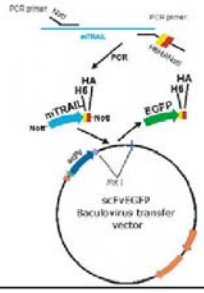


αDsg3 scFv in living mouse ear: 2 photon microscopy



Lesson 9: science is beautiful

Immunological barrier or gate
Cloning TRAIL for scFv-delivery to epidermis



Lesson 14: a team is needed for success

Stanley,Koulu, Thivolet **J Clin Invest** 1984

Koulu, Kusumi, Steinberg, Klaus-Kovtun,Stanley, **JExpMed** 1984

Eyre, Stanley, **JExpMe**d 1987

Stanley,Koulu,Klaus-Kovtun,Steinberg **J Immunol** 1986;

Korman,Eyre,Klaus-Kovtun,Stanley, **New Engl J Med** 1989

Amagai,Klaus-Kovtun, Stanley, **Cell** 1991

Anhalt,Kim,Stanley,Korman,Jabs,Kory,Izumi,RatrieIII,Mustasim,Ariss-bso,Labib, **New Engl J Med** 1990

Koch,Mahoney,Ishikawa,Pullkinin,Uitto,Shultz,Murphy,Whitaker-Menezes,Stanley, **J Cell Biol** 1997

Koch,Mahoney,Cotsarelis,Rothenberg,Lavker,Stanley **J Cell Sci** 1998

Mahoney, Wang,Rothenberger,Koch,Amagai,Stanley, **J Clin Invest** 1999

Wu,Wang,Yan,Lyle,Fakharzadeh,Wahl,Wheelock, Ishikawa,Uitto,Amagai,Stanley **New Engl J Med** 2000

Amagai,Matsuyoshi,Wang,Stanley, **Nat Med** 2000

Payne,Ishii,Kacir,Lin,Li,Hanakawa,Tsunoda,Amagai,Stanley,Siegel **J Clin Invest** 2005

Ishii,Lin,Siegel,Stanley **J Invest Dermatol** 2008; Yamagami, Stanley

Yamagami J, Payne AS, Kacir S, Ishii K, Siegel DL, Stanley JR **J Clin Invest 2010**

Lesson 15: you need financial support for success

U.S. Department of Health and Human Services

Supported by the

National Institutes of Health

NIAMS

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Lesson 16: make new lifelong friends

AZA: Clinical uses

- FDA approved for
  - Kidney transplant rejection prophylaxis
  - Rheumatoid arthritis, severe
  - Crohn's disease
  - Ulcerative colitis
- Off label dermatology uses –personal experience using
  - Immunobullous diseases
  - CTD diseases – LE, DMM, small vessel vasculitis
  - Psoriasis, lichen planus, and eczematous diseases
  - Photodermatoses
  - Urticaria and urticarial dermatitis
  - Other pruritic and oral corticosteroid responsive diseases
  - Virtually all steroid responsive skin diseases

Table 1 Licensed and unlicensed indications for azathioprine in the treatment of dermatological disorders (in Great Britain)

Licensed indications	Unlicensed indications
Systemic lupus erythematosus	Atopic dermatitis
Dermatomyositis	Psoriasis
Pemphigus vulgaris	Bullous pemphigoid
	Chronic actinic dermatitis
	Pyoderma gangrenosum
	Pityriasis rubra pilaris
	Wegener's granulomatosis
	Cutaneous vasculitis

bullous pemphigoid (Grade B; level IV)
Pemphigus vulgaris (Grade B; level II)
Severe, recalcitrant atopic dermatitis (Grade A; level I)
Chronic actinic dermatitis (Grade A; level I)
Behcet's disease (Grade A; level I)
Severe, recalcitrant psoriasis (Grade C; level IV).
Wegener's granulomatosis, pyoderma gangrenosum, pityriasis rubra pilaris,lupus erythematosus, and lichen planus (anecdotal- Grade C; level IV).

AZA: Deployment and Monitoring

- Baseline: TPMT, CMP, CBC (+/-pregnancy test),
  - *PPD (or Interferon gamma release assay), Hep B, C Serology, HIV*
- CMP, CBC bimonthly for 2 months then q3-6 months
- Complete skin exams if on AZA for more than 2 years in patients predisposed to skin cancer

Thiopurine methyltransferase activity

Table 1. Interethnic variation of TPMT activity

Group	N	Homozygous wild-type (%)	Heterozygote (%)	Homozygous mutation (%)	TPMT*2 (%)	TPMT*3A (%)	TPMT*3C (%)
American Caucasians	Calculated	92.5	7.4	0.14	0.2	3.2	0.2
British Caucasians	199	89.9	9.6	0.5	0.5	4.5	0.3
French Caucasians	191	85.9	13.6	0.5	0.5	5.7	0.8
African Americans	Calculated	90.7	9.2	0.2	0.4	0.8	2.4
South Asians	99	98	2	0	0	1	0
Ghanaians	217	85.3	14.4	0.5	0	0	7.6
Kenyans	101	89.1	10.9	0	0	0	5.4
Chinese	192	95.3	4.7	0	0	0	2.3
Japanese	553	97.3	2.4	0.4	0	0	1.5
Thai	75	89	11	0	0	0	5.3

Modified from McLeod.[40]

- Two approaches to measurement
  - RBC activity
  - genotypes
- Reason to check TPMT
  - Dosing
  - Avoidance of TPMT nulls

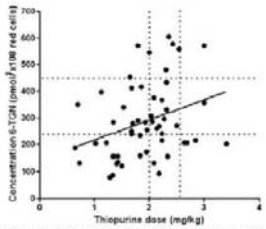


FIGURE 1. Relationship of the 6-TGN concentrations with the thiopurine dose. The 6-MP dose was calculated using a conversion factor of 2.0731. The known noncompliant patients and two outlier results were omitted. A weak correlation was present on regression analysis ($r = 0.32$; $P = 0.018$; Pearson's regression). The broken lines represent the weight-based recommended dosage (x-axis) and therapeutic range for 6-TGN (y-axis).

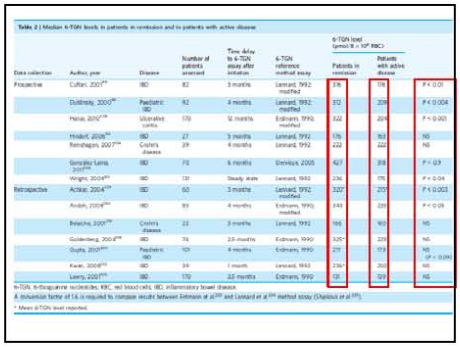
AP&T Alimentary Pharmacology and Therapeutics

Review article: the benefits of pharmacogenetics for improving thiopurine therapy in inflammatory bowel disease

L. Chouchana[*,†,‡], C. Narjoz[*,†,‡], P. Beaune[*,†,‡], M.-A. Loriot[*,†,‡] & X. Roblin[§]

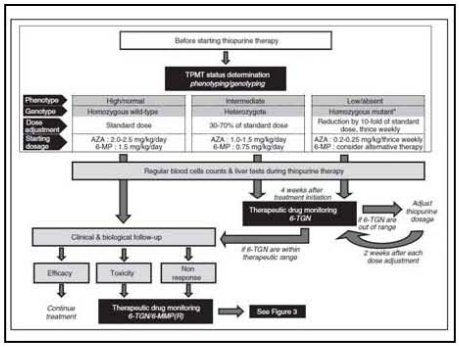
Conclusions
Based on the literature data, we provide a therapeutic algorithm for thiopurines therapy with starting dose recommendations depending on TPMT status and thereafter dose adjustments according to five metabolite profiles identified with therapeutic drug monitoring (TDM). This algorithm allows a dosage individualisation to optimise the management of patients under thiopurine. Furthermore, identification of new pharmacogenetic biomarkers is promising for ensuring maximal therapeutic response to thiopurines with a minimisation of the risk for adverse events.

Aliment Pharmacol Ther 2012; 35: 15–36



Data collection	Author, year	Disease	Number of patients assessed	Time delay to 6-TGN assay after initiation	6-TGN reference method assay	6-TGN level (pmol/8 × 10^8 RBC): Patients in remission	Patients with active disease	
Prospective	Cuffari, 2001[44]	IBD	82	3 months	Lennard, 1992; modified	316	156	P < 0.01
	Dubinsky, 2000[46]	Paediatric IBD	92	4 months	Lennard, 1992; modified	372	239	P < 0.004
	Haraz, 2012[134]	Ulcerative colitis	170	12 months	Erdmann, 1990; modified	322	204	P < 0.003
	Hindorf, 2006[45]	IBD	27	3 months	Lennard, 1992	176	163	NS
	Reinshagen, 2007[135]	Crohn's disease	39	4 months	Lennard, 1992	222	222	NS
	González-Lama, 2007[136]	IBD	70	6 months	Dervieux, 2005	427	318	P < 0.9
	Wright, 2004[137]	IBD	130	Steady state	Lennard, 1992	236	75	P < 0.04
Retrospective	Achkar, 2004[138]	IBD	60	3 months	Lennard, 1992; modified	320*	270*	P < 0.003
	Andoh, 2004[139]	IBD	89	4 months	Erdmann, 1990; modified	348	255	P < 0.05
	Belaiche, 2001[140]	Crohn's disease	22	3 months	Lennard, 1992	166	163	NS
	Goldenberg, 2004[141]	IBD	78	2.5 months	Erdmann, 1990	325*	229*	NS
	Gupta, 2007[142]	Paediatric IBD	101	4 months	Erdmann, 1990	237	173	NS (P = 0.09)
	Kwan, 2004[143]	IBD	39	1 month	Lennard, 1992	230*	202*	NS
	Lowry, 2007[144]	IBD	170	2.5 months	Erdmann, 1990	290	220	NS

6-TGN, 6-thioguanine nucleotides; RBC, red blood cells; IBD, inflammatory bowel disease.
A conversion factor of 1.6 is required to compare results between Erdmann et al.[139] and Lennard et al.[284] method assay (Dubinsky et al.[145]).
* Mean 6-TGN level reported.



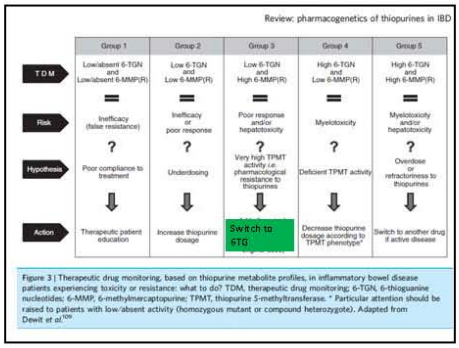


Figure 3 | Therapeutic drug monitoring, based on thiopurine metabolite profiles, in inflammatory bowel disease patients experiencing toxicity or resistance: what to do? TDM, therapeutic drug monitoring; 6-TGN, 6-thioguanine nucleotides; 6-MMP, 6-methylmercaptopurine; TPMT, thiopurine S-methyltransferase. * Particular attention should be raised to patients with low/absent activity (homozygous mutant or compound heterozygote). Adapted from Dewit et al.[106]

AZA and itch

- Few trials separately analyze response to itch
  - Atopic dermatitis trials – use SCORAD or VAS
- Only one dermatitis trial measured TP levels
  - JAAD Aug 2012 – 12 pediatric patients – only three had 6TG levels within the therapeutic range
  - Used SCORAD measure – 1/3 weighted for itch

Reasons for AZA failure

- Acute intolerance – random event seen within fist 10-20 days
- Delayed intolerance – toxic 6MMP levels
  - Malaise and nausea even with LFT elevations
- Inadequate dosing – failure to attain significant 6TG levels
- Leukopenia/cytopenias without efficacy – seen mostly in elderly patients

Azathioprine Complications - Common

- Intolerance syndrome – within first 2-4 weeks
  - Think of pancreatitis (get serum lipase)
- Hepatitis – associated with increased 6-MMP levels
- Bone marrow suppression – associated with increased 6-TG levels
- Squamous cell CA of skin – long term use

Itching: What's New

Gil Yosipovitch, MD

Chronic Itch Clinical Cases & Their Management SEC UNC Chapel Hill 2012

Gil Yosipovitch
Professor
Departments of Dermatology Neurobiology& Anatomy & Regenerative Medicine
Wake Forest University School of Medicine
Winston-Salem, NC, USA

Disclosures

- Advisory Board: GSK/Stiefel, Leo Pharma, Merck
- Consultant: J&J, Sanofi Aventis, Mitsibushi, Regneron, Cosmoderm
- Funded: NIH, Cosmoderm
- Mention off label use of several treatments

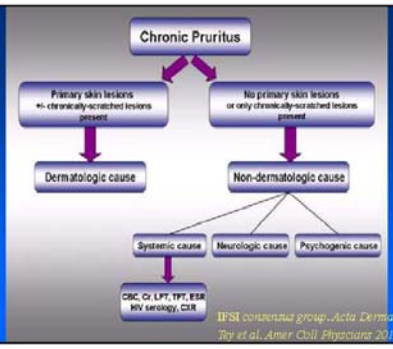
New Paradigm

- Chronic Itch is a disease state in its own right
- When itch patients receive adequate treatment for chronic itch – improvement in quality of life
- Anti-histamines in most cases do not work for chronic itch
- Aggressive therapy is required to tackle chronic itch

Yosipovitch Clin &Exper Dermatol Rez 2011

Case Number One

- 55 year old patient with severe generalized itch for 10 years VAS 7-10
- Lichenified plaques on ankles and excoriations on back
- Work up negative for underlying systemic diseases



IFSI *consensus group. Acta Dermatol 2*
Tey et al. Amer Coll Physicians 2011

CNS- Targets for Itch Treatment

- Reduction of central sensitization of itch supraspinally

1. Anti- depression drugs SNRI; Mirtazapine 15mg
2. Drugs that decrease the release of several neurotransmitters: gabapentin, pregabalin
3. Combo: Mirtazapine and Gabapentin/Pregabalin

- Opiate Kappa agonists and Mu Antagonists
- Neurokinin 1 inhibitors: Aprepitant

Tey & Yosipovitch Br J Dermatol 2011

How Do I treat Generalized Idiopathic Pruritus Without Rash

The Role of Opioids in Chronic Itch an Imbalance between μ- and κ-Receptor-Activity?

Ueraschi Het al. Eur J Pharmacol 2002
Siglioni et al. J Invest Derm 2006
Terunga & Takamori J Invest Derm 2007

A Kappa Agonist & Mu Antagonist For Intractable Chronic Itch

- Butorphanol is a analgesic inhaler FDA approved for acute pain
- Effective in treating chronic intractable itch
- Doses 1mg= 1 puff doses: 1mg up to 4 mg per day
- Disease indications: Atopic eczema, Malignancy chronic itch, Uremic
- *Dawn & Yosipovitch J Amer Acad Dermatol 2006;54:527-31.*

Aprepitant A New Antipruritic

- Aprepitant (Emend)™ antiemetic agent in chemotherapy-induced nausea and vomiting
- Substance P inhibitor
- 80mg/d 40mg bid
- Extremly expensive 160$ per pill
- Effective for
- 1. Prurigo & Atopic eczema
- 2. CTCL
- 3. Erlotnib induced itch

Dawn et al. NEJM Oct 2004 351:1-0-S1-16
Stander PLoS One. 2010 Jun 4;5:e10968

What's new in Topical Anti Pruritics

- Not Much
- Topical strontium gel 4% has antipruritic effect
- Topical Capsaicin 8% Qutenza for neuropathic itch

Double Layer Wet Pajamas

- Effective for itch reduction
- Moisturizer with low potency steroid on top a wet layer and dry layer on top
- Associated with the recovery of epidermal barrier.
- Induces clinical improvement by the release of restoration of intercellular lipid lamellar structure

J Eur Acad Dermatol Venereol. 2007;21:1360-4
Dermatol Nurs. 2005;17(5):365-7.

Severe Itch in African Americans

- 14 year old African American patient with prurigo nodules and lichenification
- Family history of similar lesions extensor involvement with severe itch

Atopic Dermatitis Is Common and Severe in African Americans

- Severe AD 70% more of Black race
- Large population study in US black race higher prevalence of AD
- Presentation of eczema differs more extensor involvement more papular and prurigo nodules

J Invest Dermatol. 2010 Aug 26
Duke et al. Ped Derm. May 2012

High Association of Infrauricle Fissure and VAS Itch Scores In Follow Up

- 29 patients who returned for follow up, the correlation coefficient between infra-auricular fissure score and VAS scores for itch intensity was 0.6 ($p<0.01$)

Kwatra et al. J. Amer Acad Dermatol. May 2012

Therapeutic Ladder for Atopic Dermatitis Itch

Azathioprine Underutilized Medication in US for AD

- Dose 1 mg/kg
- TMPT activity (thiopurine methyltransferase)
- Low levels in Blacks!!!
- Side effects: nausea, hypersensitivity
- Safe in pediatric patients

Meggitt et al. Lancet 2006 Mar 11;367:839-46
Murphy &. Atherton Pediatr Dermatol. 2003 Nov-Dec;20(6):530-4

Mycophenolate Mofetil (Cell Cept®) for Severe AD

- MMF inhibition of inosine monophosphate dehydrogenase – blocks de novo purine synthesis and
- 75 mg/kg (max 3 gr/daily)
- More than 50% full clearance or >90%.
- Initial response 8 weeks max response 8-12 weeks
- No side effects, no infections.
- No effect on cyclosporine failures
- Other indications for itch: Chronic Urticaria, Grovers Disease

Heller et al. Br J Dermatol 2007

Cognitive Approach for Treatment of Itch

- Patients' cognitive capability to control the itch-scratch can be enhanced with education, support, and cognitive and behavioral therapies
- Education:

1. Teaching itch relieving interventions
2. Use of medications.

- Support : individual and group counseling, enrolling in support groups, providing education resources,.
- Cognitive and behavioral therapies:

1 Awareness training and habit reversal,
2. Stress management education
3. Guided imagery

Tey et al. Clin Dermatol. in press 2012

Other Holistic Approaches Treating Chronic Itch

- Healing Touch - bio field therapy
- (HT) has been reported to relieve pain, stress, and anxiety.
- Mindfullness stress reduction
- Light Massage
- Yoga therapy

Danhauer SC, et al., J Soc Integr Oncol 2008; 6: 89-97.
Kemper KJ,. J Soc Integr Oncol 2009; 7: 12-8.

Curtis J. Amer Acad Dermatol. 2011 64:955-9

Case Number 4

- 45 year old patient with severe itch VAS scale of 10 out of 10. Mainly on his bilateral arms and shoulder girdle
- Patient is on large dose of opioids post back trauma.
- Patient is an avid cyclist and itch is aggravated after cycling
- Denies vehemently substance abuse
- Referred by Pain specialist for suspected opioid induced itch
- Course of naltrexone was not helpful

Pain Can Coincide With Itch In Neuropathic Itch

- Neuropathic itch can coincide with pain.
- Examples: Post Herpetic Neuralgia, Notalgia Parasthetica, brachioradial itch, prurigo nodularis.

Yosipovitch & Samuel. Dermatol Therap 2009

Brachioradial Pruritus

- Cervical root compression.
- Data of nerve conduction studies demonstrated evidence of cervical radiculopathy and spinal stenosis C6-C7.
- Photo aggravated: tennis players

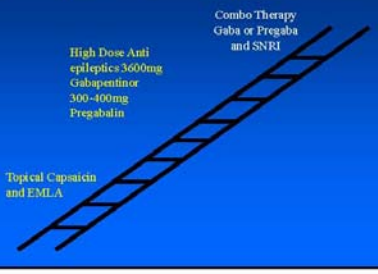
Stander et al. J Amer Acad Dermatol 2011;
Cohen et al. J Am Acad Dermatol. 2003 48: 825-8.
Goodkin et al. J Am Acad Dermatol. 2003 48: 521-4.

Localized Itch Disorders

Paresthetic algias"Respond well to Anti Epilepetics Gabapentin and Pregabalin

- **Scalp dystesthesia**
- Brachioradial
- Notalgia parasthetica
- Meralgia parasthetica
- **Vulvar and Scrotal itch**

Management of Neuropathic Itch



A Case of Senile Pruritus??

- 78 year old male 6 months of new onset itch all over his body
- No history of atopy
- Blood tests: CBC, LFT, Creat, TSH within normal limits
- Diagnosis: Senile Pruritus

Lymphomas & Lymphoreticular Malignancies Can Cause Severe Itch

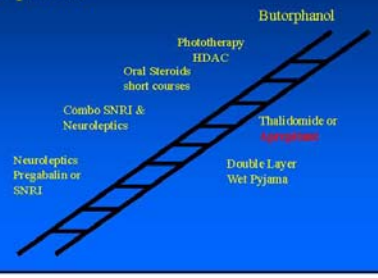
- Mycosis fungoides- erythrodermic forms
- Hodgkins & NHL Lymphoma
- Myelodyspalstic syndrome
- Multiple Myeloma
- Solid Tumors : hepatic, pancreatic

What`s New in Pathophysiology of CTCL itch

- Interleukin 31 is a pruritogenic mediator recently found to be elevated in CTCL

Olmatsu et al
Acta Dermatol Venreol May 2012

Therapeutic Ladder for Itch in Lymphoma



What's New in Dermatopathology

Dan Zedek, MD

What's New in Dermatopathology (and how it relates to you in practice)

Dan Zedek, MD
Director of UNC Dermatopathology

Eosinophilic Dermatosis of Hematologic Malignancy

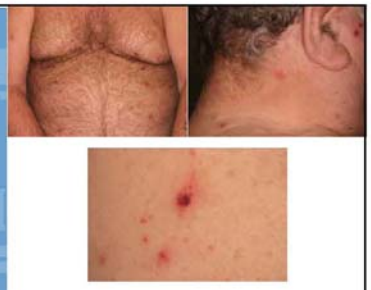
- First described in 1965 by Weed as an insect-bite like reaction observed in patients with chronic lymphocytic leukemia (CLL)
- Thought initially to be a specific hypersensitivity reaction to insect bites, but most patients cannot recall being bitten

Eosinophilic Dermatosis of Hematologic Malignancy

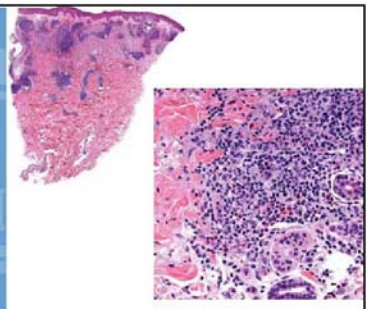
- Proposed Criteria:
  - Pruritic papules, nodules, and/or vesiculobullous eruption refractory to standard treatment
  - Histopathology revealing eosinophil-rich superficial and deep dermal lymphohistiocytic infiltrate
  - Exclusion of other causes of tissue eosinophilia
  - Diagnosis of hematologic malignancy
    - Described in CLL, other B-cell lymphomas/ leukemias, AML, and myelofibrosis

Eosinophilic Dermatosis of Hematologic Malignancy

- Clinical Manifestations:
  - 5-7th decade of life
  - Eruption occurs concurrent with or months to years after diagnosis of malignancy (can occasionally precede diagnosis of malignancy)
  - Pruritic, frequently tender papules, nodules, and in some cases vesicles/bullae occurring in both exposed and non-exposed sites including face, trunk, and extremities
  - Lesions are often indurated and erythematous
  - In most cases, no relationship with outdoor activity and no history of insect bites or seasonal changes



Journal of Cutaneous Pathology
Volume 39, Issue 7, pages 650-656, 22 MAY 2012 DOI: 10.1111/j.1600-0560.2012.01926.x



Journal of Cutaneous Pathology
Volume 39, Issue 7, pages 650-656, 22 MAY 2012 DOI: 10.1111/j.1600-0560.2012.01926.x

Eosinophilic Dermatosis of Hematologic Malignancy

- Differential diagnosis:
  - Arthropod assault/papular urticaria/scabies
  - Drug eruption
  - Urticarial stage of bullous pemphigoid
  - Eosinophilic folliculitis
  - Dermatitis herpetiformis
  - Wells syndrome
  - Leukemia cutis

Eosinophilic Dermatosis of Hematologic Malignancy

- A variety of treatment options have been tried:
  - Antibiotics, topical and systemic steroids, antihistamines, dapsone, phototherapy, radiation, interferon alpha, IVIG, re-initiating chemotherapy
- For the most part, results have been disappointing
- Eosinophilic dermatosis of hematologic malignancy may be associated with a more aggressive CLL-disease course
- Pathogenesis is poorly understood

Eosinophilic Dermatosis of Hematologic Malignancy

- **References:**

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Cutaneous Manifestations of CLL

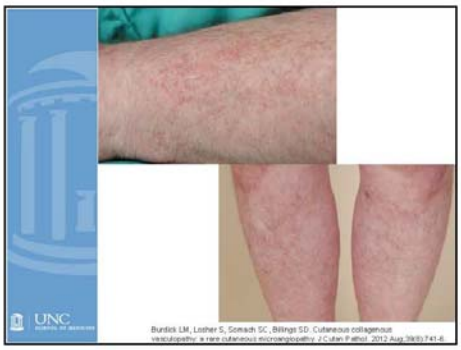
- CLL reportedly involves the skin as leukemia cutis in 8.3% of patients with CLL
  - Red-brown papules or nodules
- Non-specific eruptions (not leukemia cutis) occur in 45% of CLL patients and include:
  - Petechiae
  - Purpura
  - Urticaria
  - Erythema multiforme
  - Exfoliative dermatitis
  - Paraneoplastic pemphigus
  - Eosinophilic dermatosis of hematologic malignancy

Cutaneous Collagenous Vasculopathy

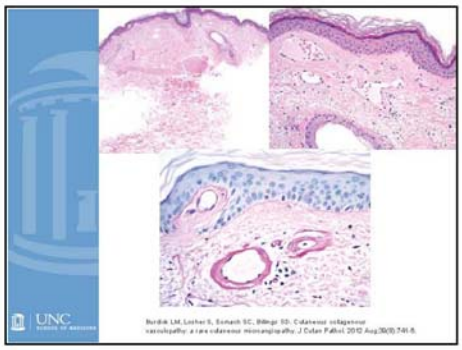
- Rare microangiopathy of superficial dermal blood vessels
- Telangiectatic blanchable non-urticating macules, predominantly on the extremities, reminiscent of generalized essential telangiectasia
- Usually symmetrical
- Typically macules begin on lower extremities and progress to trunk and upper extremities

Cutaneous Collagenous Vasculopathy

- More common in men, usually middle-age to older but has been reported in children and women
- Microscopic Findings:
  - Dilated, thick-walled vessels without significant hemorrhage or an inflammatory infiltrate
  - Vessel walls contain amorphous, hyaline material which is PAS positive (basement membrane type IV collagen)



Burdick LM, Lother S, Somach SC, Billings SD. Cutaneous collagenous vasculopathy: a rare cutaneous microangiopathy. J Cutan Pathol. 2012 Aug;39(8):741-6.



Burdick LM, Lother S, Somach SC, Billings SD. Cutaneous collagenous vasculopathy: a rare cutaneous microangiopathy. J Cutan Pathol. 2012 Aug;39(8):741-6.

Sebaceous lesions and Muir-Torre syndrome

- Familial MTS is a variant of hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome
- Usually autosomal dominant
- High degree of penetrance
- Variable expression
- Can be sporadic
- Sebaceous tumors, keratoacanthomas, epidermal cysts, and colonic polyps in association with visceral neoplasms such as gastrointestinal carcinomas

Muir-Torre syndrome

- Familial cases are due to a defect of a DNA mismatch repair (MMR) gene.
- A mutated allele is inherited (first hit) then a somatic loss-of-function alteration of the remaining wild-type allele (second hit) must happen.
- Inactivation of both alleles entails microsatellite instability due to the inability to correctly repair DNA mutations.
- The MMR proteins mainly related to MTS are, MLH1, MSH2, MSH6, and PMS2

Muir-Torre syndrome

- **Suggested diagnostic criteria for MuireTorre syndrome**

Group A
- Sebaceous adenoma
- Sebaceous epithelioma
- Sebaceous carcinoma
- Keratoacanthoma with sebaceous differentiation

Group B
- Visceral malignancy

Group C
- Multiple keratoacanthomas
- Multiple visceral malignancies
- Family history of MuireTorre syndrome

In order to achieve a diagnosis of MuireTorre syndrome, the patient must fulfill one criterion each from groups A and B or fulfill all three criteria from group C.

Schwartz RA, Torre DP. The Muir-Torre syndrome: a 25-year retrospect. J Am Acad Dermatol. 1995;33:90-104.

Sebaceous lesions and Muir-Torre syndrome

- Among the visceral malignancies involved, the most commonly found are carcinomas of
  - Colon (accounting for 50% of all malignancies)
  - Genitourinary tract (21%)
  - Breast (12%)
  - Hematologic Malignancy (9%)
  - Endometrium
  - Ovary

Sebaceous lesions and Muir-Torre syndrome

- ~ 50% of patients with MTS have 2 or more visceral malignancies
- Although the internal malignancies associated with MTS generally metastasize more often, median survival appears to be significantly longer than for those not associated with MTS

Sebaceous lesions and Muir-Torre syndrome

- 56% of MTS cutaneous lesions appear after a visceral malignancy is diagnosed
- 22%–32% of the cutaneous lesions are the first manifestation of MTS
- 6%–12% appear concomitantly
- A cutaneous tumor can appear several decades before or after the internal malignancy

Sebaceous lesions and Muir-Torre syndrome

- Sebaceous adenoma: found in 25-68% of patients with MTS
- Sebaceoma: found in 31-86% of patients with MTS
- Sebaceous carcinoma: found in 66-100% of patients with MTS
- Sebaceous hyperplasia and nevus sebaceus are generally excluded from MTS
- While still controversial, most experts recommend testing for MTS in patients with a sebaceous adenoma, sebaceoma, or sebaceous carcinoma

Sebaceous lesions and Muir-Torre syndrome

- Some studies initially recommended only testing patients with sebaceous lesions who were <50 and/or have lesions below the neck
- However, more recent studies have found sebaceous lesions and internal malignancies can occur and be the initial presentation after the 5th decade of life and commonly occur on the head and neck region so testing all sebaceous lesions at any age seems to be the recommended current approach
- The mean age for presentation with a sebaceous neoplasm in one study was 63 years (range, 37-85 years)

Sebaceous lesions and Muir-Torre syndrome

- Testing is generally not recommended for a single keratoacanthoma but is recommended for multiple keratoacanthomas, especially if there is a concerning personal or family history

Sebaceous lesions and Muir-Torre syndrome

- Many papers now recommend immunohistochemical staining to screen for loss of MLH1, MSH2, MSH6, and PMS2 in the sebaceous neoplasm.
- The positive predictive value is reported as:
  - MLH1: 88%
  - MSH2: 55%
  - MSH6: 67%
- Knowing which protein is lost can also help identify which gene to sequence to look for germline mutations

Sebaceous lesions and Muir-Torre syndrome

- Microsatellite instability can also be detected by molecular testing as an alternative to immunohistochemistry
- Generally similar sensitivity and agreement with immunohistochemistry
- Which is the best screening method is controversial but many recommend immunohistochemistry because of ease of use and relatively low cost

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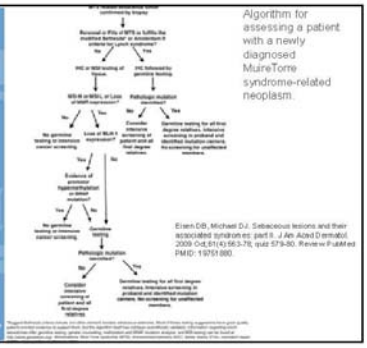

Algorithm for assessing a patient with a newly diagnosed MuireTorre syndrome-related neoplasm.

Eisen DB, Michael DJ. Sebaceous lesions and their associated syndromes: part II. J Am Acad Dermatol. 2009 Oct;61(4):563-78; quiz 579-80. Review PubMed PMID: 19751880.

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Germline Mutational Testing in MTS

- The sensitivity of germline mutation analysis ranges from 50% to 95% depending on the methodology. For patients in whom a mutation is identified, the sensitivity for the proband's family is nearly 100%, and significantly less expensive than the initial analysis

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Sebaceous lesions and Muir-Torre syndrome

- **References:**

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- Eisen DB, Michael DJ. Sebaceous lesions and their associated syndromes: part II. J Am Acad Dermatol. 2009 Oct;61(4):563-78; quiz 579-80. Review. PubMed PMID: 19751880.

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Questions?

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Surgical and Medical Management of High-Risk Skin Tumors

Puneet Jolly, MD, PhD
Brad Merritt, MD

Medical and Surgical Management of High Risk Skin Cancer

Puneet S. Jolly MD, PhD and Bradley G. Merritt, MD
University of North Carolina
Department of Dermatology

Epidemiology

- SCC/BCC account for >90% of skin CA in transplant patients
- Incidence increases with *duration* and *extent* of immunosuppression
- more than **50%** of **Caucasian** transplant patients will develop skin CA
- SCC is between **65-250x** more likely while BCC is **10x** more likely
- BCC:SCC is **4:1** in non-transplant but **1:4** in transplant patients
- Age – 40yo – mean is *8yrs* to develop 1st cancer while 60yo – mean is *3yrs* to develop 1st cancer. Mean interval is 15mo between 1st and 2nd skin CA and 11mo between 2nd and 3rd.
- Keratoacanthomas in transplant patients are difficult to distinguish from SCC – *KAs in transplant should be treated like SCC*!
- Age and distribution of skin CA – if transplant before 40yo, 80% of tumors are on *dorsal hands/arms, upper trunk*
- if transplant after 50yo, 80% are on *head and neck*
- SCC in transplant patients are more aggressive - ~ 13% recurrence rate and 8-10% metastasize
- Poor prognosis – SCC on head, older age, history of extensive sun exposure

Risk Factors

- History of UV exposure (***SCC before transplant***)
- Degree of immunosuppression ***(Triple drug >> Double drug)***
- lower CD4 counts in patients with CA than patients without
- Age at transplantation

• History of lymphoma

• HPV – DNA detected in 65-90% of skin CA in transplant pts.

Histologic Features of Skin Cancer in Transplant Patients

AK	SCC	BCC	Melanoma	Kaposi
• Bacterial colonization • confluent parakeratosis • verrucous changes	• Acantholysis • Infiltrative growth(deeper) • More spindle cell variant • Features of ***HPV infection*** (koilocytes, verrucous change, hypergranulosis) • Ectatic superficial vessels	• mostly Superficial BCC • less dense inflammatory infiltrate • younger males • also in sun-protected areas (genitalia/axilla)	• mostly men • trunk > upper limbs > H&N • mostly deeper (> 0.76 mm Breslow)	• more aggressive • Resembles classic KS (multiple lesions on legs) • w/greater immuno-suppression looks like KS in AIDS patients

Pathogenesis

• Decreased immune surveillance (decreased langerhans cells) - due to immunosuppressive medications and UV radiation

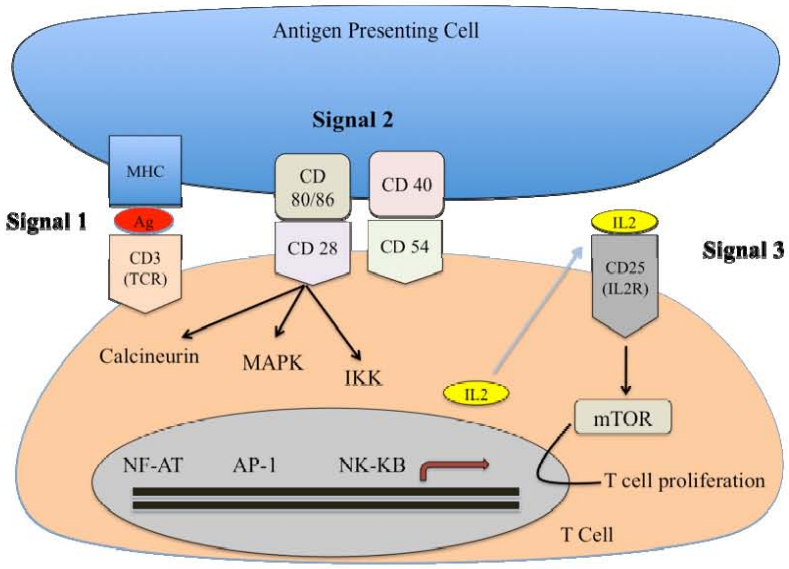
• Depressed *NK cell function*

• UV induces DNA damage but may actually cause even more profound immunosuppression *(LH cells, cis-urocainic acid)*

• HPV 16/18 and 5/8 (*EDV*) are expressed at significantly higher level in OTR patients than non-OTR patients

• Medication-specific effects

Targets for Immunosuppressive Medications



Approach to Immunosuppression

Class A	Class B	Class C	Class D
Steroids	Cyclosporine Tacrolimus	Imuran Cellcept	Sirolimus Everolimus

- Class A and C had been used together for many years
- Class A and B used with less side effects
- In some patients need to use Class A/B/C together
- Class D now used to replace Class B and C

mTOR Inhibitors (Sirolimus/Everolimus)

- non-nephrotoxic immunosuppressant with antitumoral and antiangiogenic properties
- reduced incidence of malignancy posttransplantation
- Antiangiogenic agent in the progression of Kaposi sarcoma (KS) offers an alternative therapeutic option for transplant-associated KS

SIDE EFFECTS -

- Impaired wound healing, Proteinuria, Edema, Pneumonitis, Thrombotic microangiopathy
-
- Cannot use together with CsA/Tacrolimus b/c of *nephrotoxicity, HUS, significant hypertension*

Approach to Treatment

Suggested Follow-up Skin Exam in OTR

Risk Factors	Interval F/U (Months)
No skin cancer	12
Actinic Keratoses (Field Disease)	3-6
1 NMSC	3-6
Multiple NMSCs	3
High Risk SCC/Melanoma	3
Metastatic SCC/Melanoma	1-3

Actinic Keratoses and Warts

- Cryotherapy, 5-FU, ED&C, Aldara, PDT, Ablative skin resurfacing

"Field Cancerization"

- Cyclic rotation of PDT, 5-FU, Aldara
- **5-FU** – decreases size & number of lesions. *Works better if combined with alpha/beta hydroxyacids or tretinoin*
- Aldara – recent review showed safe in areas of up to 5x5cm (3x/week for 16 weeks). Helps clear "dysplasia" (AKs and warts)
- **Photodynamic therapy** - AKs and superficial NMSC
  - pre-treatment debridement of hyperkeratotic lesions and use of the red light may lead to an improved clinical response
  - Studies have shown better compliance, better cosmetic outcomes with PDT rather than efudex.

Higher Risk Skin Cancer

- Size > 0.6 cm in "mask" area on face (central face, eyelids/eyebrows, nose, lips, chin, temple, ear)
- > 1cm on cheeks, forehead, scalp and neck
- > 2cm on trunk and extremities
- Indistinct borders
- Ulceration
- Location (genitalia, digits)
- Within scar/radiation site
- Recurrence

Management of Higher Risk SCCs

- ***Mohs*** or aggressive surgical therapy (6-10mm margins)
- Consider adjuvant XRT for deep lesions or near parotid
- Recurrence/metastasis - >6mm thickness, desmoplastic growth, perineural invasion
- ? Elective nodal resection vs XRT
- Clinical involvement of cervical nodes should undergo elective neck dissection

Chemoprevention - Retinoids

Indications	Contraindications
• 5-10 NMSCs per year (fewer if "high risk" SCC • Eruptive KAs • SCC with high metastatic risk • Metastatic SCC • OTR w/history of lymphoma/ leukemia and SCC	• Pregnancy and lactation • women of childbearing age • severe renal/hepatic dysfunction • uncontrolled hyperlipidemia • concomitant hepatotoxic meds/ EtOH

- Start at *10mg* Soriatane PO qdaily
- Increase slowly by *10mg* increments until achieve desired effects
- 0.3-0.4mg/kg/day (Soriatane)
- 0.25mg/kg/day for 2mo then up to 0.5mg/kg/day (Isotretinoin)
- Need to maintain patients on retinoids b/c severe rebound can occur if discontinue
- Can use higher doses with concomitant chemotherapy in patients with metastatic disease

Other Systemic Therapies

- EGFR inhibitors
- Systemic 5-FU (Capecitabine)
- Vizmodegib for BCC

Surgical Management to be Discussed as Case Presentations

2012 SEC Accepted Abstract/Poster Presentations:

(in alphabetical order by corresponding author)

Poster Number	Corresponding Author	Institution	Presentation Category	Abstract Title
18	Al-Dabagh, Amir, BS Axa499@case.edu	Case Western Reserve University	Medical Dermatology	Underuse of Early Follow-Up Visits: A Missed Opportunity to Improve Patients' Adherence
1	Al Dabagh, Bishr, MD Bishr.aldabagh@duke.edu	Duke University Medical Center	Procedural Dermatology	Mohs Surgery for Basal Cell Tumors in Patients Undergoing Treatment with Vismodegib
20	Rachel Blasiak, BS Rachel_blasiak@med.unc.edu	University of North Carolina at Chapel Hill	Medical Dermatology	Does Sunscreen Use Decrease the Incidence of Primary Cutaneous Melanoma in Caucasians: A Systematic Review
25	De Golian, Emily, BS emilydegolian@gmail.com	Medical College of Georgia	Medical Dermatology	Atypical Fibroxanthomas in an African American Patient with Xeroderma Pigmentosum
2	Ferrero, Natalie, BS Natalie_ferrero@med.unc.edu	University of North Carolina at Chapel Hill	Medical Dermatology	Skin Scan: A Demonstration of the Need for FDA Regulation of Medical Apps on iPhone
28	Glover, Mary, MD mglover@georgiahealth.edu	Medical College of Georgia	Medical Dermatology	The Full Spectrum of Cutaneous Manifestations in Homozygous Familial Hypercholesterolemia
19	Graves, Michael, MD migraves@georgiahealth.edu	Medical College of Georgia	Medical Dermatology	Doxycycline Therapy in the Treatment of Reticular Erythematous Mucinosis
13	Greenhaw, Bradley, MD greenhaw@musc.edu	Medical University of South Carolina	Medical Dermatology	Viral Associated Trichodysplasia: A Case in a Cardiac Transplant Patient
24	Hess, Jaclyn, BS Jaclyn_hess@med.unc.edu	University of North Carolina at Chapel Hill	Medical Dermatology	Psoriasis in the Elderly
26	Kinney, Megan, MD mkinney@wakehealth.edu	Wake Forest University	Medical Dermatology / Dermatopathology	An Unusual Variant of Indeterminate Cell Histiocytosis

Poster Number	Corresponding Author	Institution	Presentation Category	Abstract Title
14	Kosari, Payman, MD pkosari@wakehealth.edu	Wake Forest University	Medical Dermatology / Dermatopathology	Kaposi Sarcoma in a Previously Undiagnosed AIDS Patient
12	Lewis, Francesca, MD weissf@musc.edu	Medical University of South Carolina	Medical Dermatology	A Case of Infantile Hutchinson Gilford Progeria Syndrome
23	Lin, James, BS linjr@evms.edu	Eastern Virginia Medical School	Medical Dermatology	Malignant Melanoma in the Gallbladder – Primary or Metastasis?
3	Miedema, Jayson, MD jmiedema@unch.unc.edu	University of North Carolina at Chapel Hill	Dermatopathology	Malignant Metastatic Adnexal Neoplasm Consistent with Spiradenocarcinoma Occurring in an 8 Year Old Male
22	Morris, Kristyn, BS morriskd@evms.edu	Eastern Virginia Medical School	Medical Dermatology	Lichen Planus Colocalized with Depigmentation
8	Moye, Virginia, BS vamoye@med.unc.edu	University of North Carolina at Chapel Hill	Medical Dermatology	Delayed Diagnosis of Crusted Scabies in a Down's Syndrome Patient Receiving Methotrexate for Presumed Atopic Dermatitis
16	O'Neill, Jenna, MD jeoneill@wakehealth.edu	Wake Forest University	Medical Dermatology	Basal Cell Carcinoma Arising in a Congenital Linear Nevus Sebaceous
6	Ortega-Loayza, Alex MD Aortegaloayza2@mcvh-vcu.edu	Virginia Commonwealth University	Medical Dermatology	Diagnosing an Enlarging Facial Plaque: KOH a Familiar Diagnostic Tool
29	Paul, Joan, MD joannypaul@gmail.com	Eastern Virginia Medical School	Medical Dermatology	Paraneoplastic Lipoatrophy as the Initial Presentation of a Cutaneous Marginal Zone B-Cell Lymphoma
7	Portal, Christina, MS Cep2a@virginia.edu	University of Virginia	Medical Dermatology	Cutaneous Manifestations of Intravenous Drug Use
21	Roman, Carly, BS Cjr56@case.edu	Case Western Reserve University	Medical Dermatology	Skin Cancer Knowledge and Skin Self-Examinations in the Hispanic Population of North Carolina: The Patient's Perspective
15	Rush, Patrick, BS Patrick.s.rush@gmail.com	Eastern Virginia Medical School	Medical Dermatology	Acute Generalized Exanthematous Pustulosis (AGEP) Induced by Exemestane

Poster Number	Corresponding Author	Institution	Presentation Category	Abstract Title
17	Sandoval, Laura, DO lsandova@wakehealth.edu	Wake Forest University	Medical Dermatology	Vitamin D Deficiency in the Outpatient Setting: An Analysis of US Nationally Representative Data
30	Sawardekar, Shilpa, MD Sss195@gmail.com	Eastern Virginia Medical School	Medical Dermatology	Brisk Improvement of von Zumbusch Generalized Pustular Psoriasis with Infliximab
27	Shipp, Lyndsay, MD lshipp@georgiahealth.edu	Medical College of Georgia	Medical Dermatology	Your Manicure and the Risk for Cutaneous Malignancy
9	Strowd, Lindsay, MD lchaney@wakehealth.edu	Wake Forest University	Medical Dermatology	A Decade of Dermatology Consults: Analysis of Inpatient Dermatology Consults from 2001-2011
10	Tcheung, Janet, MD j.tcheung@duke.edu	Duke University Medical Center	Medical Dermatology	Annular Lichenoid Dermatitis of Youth
11	Tcheung, Janet, MD j.tcheung@duke.edu	Duke University Medical Center	Dermatopathology	Histopathologic Features of 9 Cases of Pediatric head and Neck Melanoma
4	Vass, Audrey,BS vassas@mymail.vcu.edu	Virginia Commonwealth University	Medical Dermatology	Parchment-Like Membrane in a Newborn: A Case of a Collodion Baby
5	Yentzer, Brad, MD byentzer@wakehealth.edu	Wake Forest University	Other – Medical Economics	The Economics of Commuting for Phototherapy: Patient Incentives for Home-Based Phototherapy

2012 SEC Dermatology Poster Abstracts

Abstract 1:
MOHS SURGERY FOR BASAL CELL TUMORS IN PATIENTS UNDERGOING TREATMENT WITH VISMODEGIB

Bishr Al Dabagh (a), Justin Yu (b), Luke Perkocha (c), Sarah Arron (c)
Duke University Medical Center (a), St. Louis University (b), University of California – San Francisco (c).

Vismodegib (GDC-0449, Genetech) is a first in-class hedgehog pathway inhibitor and has been shown in human trials to reduce tumor burden in patients with advanced and metastatic BCC. We describe the histologic characteristics of three basal cell carcinomas in two patients with suspected and confirmed BCNs on Vismodegib chemotherapy. Both paraffin and frozen tissue slides were examined and no noteworthy differences were found between these BCCs and BCCs biopsied before treatment. The number of Mohs stages required for tumor clearance was similar between the pre and post drug BCCs and the Mohs frozen tissue histology was similar as well. No irregular or asymmetric features were noted and the tumors appeared contiguous.

Abstract 2:
SKIN SCAN: A DEMONSTRATION OF THE NEED FOR FDA REGULATION OF MEDICAL APPS ON iPHONE

Natalie Ferrero (a), Craig Burkhart (a), Dean Morrell (a)
University of North Carolina at Chapel Hill (a)

Background: Numerous applications are available to the public which claim to offer assistance in diagnosis and management with respect to multiple aspects of one's health, although the diagnosis and treatment advice offered may put one's health at significant risk. As a case in point, this study analyzed a specific application, Skin Scan, to determine its sensitivity for detecting melanoma.

Materials and Methods: Using the Skin Scan app, 93 photos of biopsy-proven melanoma were analyzed. Photos were obtained from Visual Dx, UpToDate, the National Cancer Institute, and Fitzpatrick's Dermatology in General Medicine.

Results Approximately 10.8% of biopsy-proven melanomas were reported as high risk lesions, 88.2% of the melanomas were reported as medium risk, and 1.2% of the melanomas were reported to be low risk lesions. The app was frequently "unable to analyze" lesions despite repeated attempts (11% of lesions in Visual Dx).

Conclusions The dismal sensitivity of Skin Scan to report melanoma as high risk, as well as the dangerous advice offered for lesion management, crystallizes why the FDA must protect the unknowing consumer and provide regulation.

Abstract 3:

MALIGNANT METASTATIC ADNEXAL NEOPLASM CONSISTENT WITH SPIRADENOCARCINOMA OCCURRING IN AN 8 YEAR OLD MALE

Jayson Miedema (a), Eric Burgon (a), Craig Burkhart (a), Karyn Stitzenberg (a), John Hipps (a), Daniel Zedek (a)
University of North Carolina at Chapel Hill (a).

We recently saw the case of an 8 year old male with histological findings of a malignant adnexal neoplasm consistent with spiradenocarcinoma. Malignant adnexal neoplasms in children are exceedingly rare and cases of spiradenocarcinoma in children are absent in the literature; unique to our case is the presentation of this rare lesion in a young child. He had an original biopsy of a chest lesion two years prior to his presentation at our institution which was interpreted as benign. However, when the lesion re-grew, a repeat biopsy was performed demonstrating ominous findings, prompting a re-excision. This re-excision demonstrated an area with significant necrosis, many mitoses, and cellular pleomorphism apparently arising out of a sharply demarcated adjacent lower-grade area. This patient's history as well as the histological features of his lesion were consistent with spiradenocarcinoma arising out of a pre-existing spiradenoma. Staging studies demonstrated multiple bilateral pulmonary nodules which were confirmed by thoracoscopic biopsy to be metastatic disease. In this age group, this tumor is fantastically rare.

Abstract 4:

PARCHMENT-LIKE MEMBRANE IN A NEWBORN: A CASE OF A COLLODION BABY

Audrey Vass (a), Sheila Krishna (a), Alex Ortega-Loayza (a), Erin Reese (a)
Virginia Commonwealth University (a).

The autosomal recessive congenital icthyoses (ARCI) are a rare group of inherited skin disorders. We herein report a case of this condition and discuss the revised nomenclature and classification of the inherited ichthyoses.

An African-American female was born with a collodion membrane. The child was born at term via spontaneous vaginal delivery to a 19 year-old primagravida with an uncomplicated pregnancy. There was no history of consanguinity or family history of skin disease. At birth, the infant was noted to be encased in a tight, transparent, parchment-like membrane with diffuse erythema with areas of fissuring. Other associated findings included ectropion, eclabium, and minor contractures of the hands, feet, ears. The nails and hair were normal. The infant was managed with emollients and prophylactic antibiotics.

Under the Revised Nomenclature and Classification of Inherited Ichthyoses established in 2009, the ARCI include congenital ichthyosiform erythroderma, lamellar ichthyosis, and harlequin fetus. These conditions all present as a collodion baby and require follow up once shedding of the membrane has occurred to determine the exact phenotype. In this patient, subsequent evaluation revealed a phenotype most consistent with congenital ichthyosiform erythroderma.

Abstract 5:

THE ECONOMICS OF COMMUTING FOR PHOTOTHERAPY: PATIENT INCENTIVES FOR HOME-BASED PHOTOTHERAPY

Brad Yentzer (a), Cheryl Gustafson (b), Steven Feldman (a)
Wake Forest University (a), Emory University (b).

Background: Although phototherapy is a safe and cost-effective treatment modality for psoriasis, economic disincentives discourage use, including both direct and indirect costs to the patient.

Purpose: To determine when it may be cost-effective for patients to purchase a home light unit versus driving to clinic for outpatient phototherapy sessions.

Methods: The estimated expenses associated with 3 months of outpatient phototherapy were determined and compared to the price of a home phototherapy unit. Factors examined included the cost of gasoline (based on the national average), fuel efficiency of the vehicle, cost of owning and operating a motor vehicle, lost wages, and copayments.

Results: The cost for a home unit is approximately $2500. Direct and indirect expenses imposed on patients increase with distance travelled to the dermatologist. If a patient lives 20 or more miles away from the dermatologist, the expenses associated with travel can total more than the expected out of pocket expense of purchasing a home phototherapy unit.

Conclusions: It may be beneficial for physicians to educate patients on the cost-burden of in-office versus home phototherapy, as patients can use these parameters to determine which option would be more cost-effective for them.

Abstract 6:

DIAGNOSING AN ENLARGING FACIAL PLAQUE: KOH A FAMILIAR DIAGNOSTIC TOOL

Alex Ortega-Loayza (a), Raj Agarwal (a), Julia Nunley (a), Calvin McCall (a)
Virginia Commonwealth University (a).

A 65 year-old male presented with a 10 month history of an enlarging facial plaque. A previous skin biopsy revealed folliculitis and abscess for which he was prescribed oral and topical antibiotics. Imaging revealed a pleural effusion and mass on the lingula; subsequent lung biopsy was concerning for tuberculosis. His providers considered scrofuloderma. Despite negative PPD and cultures, he was started on anti-tuberculosis therapy. Repeat skin biopsy and cultures indicated an acute and chronic folliculitis, candidiasis, and polymicrobial infection; fungal and AFB cultures were negative. An infectious disease specialist recommended a prolonged course of antibiotics and a dermatology consult. In our clinic a KOH preparation showed broad based, budding yeast suggestive of blastomycosis. Skin biopsy revealed pseudoepitheliomatous hyperplasia, neutrophilic abscesses, and yeast. Fungal culture confirmed *Blastomyces dermatitidis*. After one month of itraconazole therapy, the patient was improving clinically. The definitive diagnosis of blastomycosis requires a positive culture. However, the visualization of budding yeast on KOH prompted the initiation of therapy. When deep fungal infection is suspected, KOH is a quick, easy and inexpensive diagnostic tool.

Abstract 7:

CUTANEOUS MANIFESTATIONS OF INTRAVENOUS DRUG USE

Christina Portal (a), Amy Fox (b)
University of Virginia (a), University of North Carolina at Chapel Hill (b).

Intravenous drug use results in innumerable medical consequences. Cutaneous effects can be some of the first signs of addiction in a patient. Understanding and recognizing these dermatological sequelae are important in helping to treat this population. While these manifestations are dependent on the drug, preparation and severity of addiction, greater than three-quarters of drug users will have dermatological consequences.

We present two cases demonstrating distinct cutaneous sequelae of drug use.

21 yr old female with history of intravenous heroin use presented with subcutaneous nodules and ulcerations on the lower extremities at the site of venous access. Biopsy of a subcutaneous nodule revealed a foreign body granulomatous reaction. Tissue culture was negative for fungal or atypical organisms. This histological finding is consistent with an inflammatory reaction to containments often mixed with the drug.

52 yr old female presented with retiform purpura and necrosis with a history of cocaine use. The patient had classic clinical features of levamisole necrosis including involvement of helical rim and nasal tip. She had positive ANCA and ANA. Biopsy was consistent with small vessel thrombotic vasculopathy.

This poster will discuss the common dermatological manifestations of drug abusers and important diagnostic and treatment considerations.

Abstract 8:

DELAYED DIAGNOSIS OF CRUSTED SCABIES IN A DOWN'S SYNDROME PATIENT RECEIVING METHOTREXATE FOR PRESUMED ATOPIC DERMATITIS

Virginia Moye (a), Katherine Roy (a), Amy Fox (a)
University of North Carolina at Chapel Hill (a).

Sarcoptes scabiei, believed to infect 5% of the world's population, typically produces a pruritic eruption due to skin infestation by fewer than 100 mites. Crusted scabies is a severe and rare variant in which thousands to millions of mites are present. Given the high organism burden, crusted scabies is highly contagious, making early detection essential. Nonetheless, diagnosis is often delayed due to low clinical suspicion. We present a dramatic case of crusted scabies in a young male with Down's syndrome receiving treatment by a community dermatologist for presumed atopic dermatitis. On initial presentation, his mother reported a pruritic rash of ten years duration for which he most recently tried oral methotrexate without relief. He had no history of dermatitis before age 16. At his initial appointment, methotrexate was discontinued, and he was started on antibiotics, antihistamines, and topical steroids. He was then seen urgently in our clinic four weeks later because of a significant flare. Due to his highly atypical clinical presentation, the diagnosis of crusted scabies was considered and confirmed with a scabies prep.

Abstract 9:

A DECADE OF DERMATOLOGY CONSULTS: ANALYSIS OF INPATIENT DERMATOLOGY CONSULTS FROM 2001-2011

Lindsay Strowd (a), Alyssa Daniel (a)
Wake Forest University (a).

While most major academic institutions have some degree of inpatient dermatology consult service, many non-academic centers do not have reliable access to inpatient dermatologists. We sought to characterize the frequency and variety of inpatient dermatology consults seen over a ten-year period at Wake Forest Baptist Medical Center, an 885 licensed bed tertiary care hospital. We analyzed total number of consults seen each year and each month, percentage of consults that required skin biopsy for confirmation, and most common inpatient dermatology consult diagnoses. We reviewed over 3,500 consult cases from 2001 to 2011. The most common reason for dermatology consult was either for a drug eruption or cutaneous infection. The ten most common diagnoses when combined comprised greater than half of the total number of consults. We plan to further analyze this database to determine what percent of consults had a change in patient diagnosis due to an inpatient dermatology evaluation. This data helps support the importance of access to inpatient dermatology services for larger medical centers.

Abstract 10:

ANNULAR LICHENOID DERMATITIS OF YOUTH

Janet Tcheung (a), Maria Angelica Selim (a), Diana McShane (a)
Duke University Medical Center (a).

An 11 year old, otherwise healthy male, presented with a red plaque that had central lightening on the right lower leg. It had been present for at least 6 months and had mild pruritus. He had treated this plaque with clotrimazole, hydrocortisone, and econazole prior to presentation, without reprieve. KOH of the lesion was sparsely positive; therefore, Naftifine was initiated. Naftifine had minimized but not completely cleared the erythema of the outer rim. Terbinafine orally, subsequently, for 2 weeks was not helpful. He then had bacterial and fungal cultures, which were both negative. Biopsy revealed few necrotic keratinocytes at the quadrangularly-shaped rete ridges, vacuolar changes at dermo-epidermo junction, and bandlike lichenoid infiltrate in papillary dermis—these findings were consistent with Annular Lichenoid Dermatitis of Youth. Fluocinonide 0.05% ointment was initiated, and after use for 4 weeks, he had improvement, without recurrence for 10 months. This case highlights the importance of having this differential on one's radar and the difficulty in treatment, with recurrence likely.

Abstract 11:

HISTOPATHOLOGIC FEATURES OF 9 CASES OF PEDIATRIC HEAD AND NECK MELANOMA

Janet Tcheung (a), Kelly Nelson (a), Puja Puri (a)
Duke University Medical Center (a).

Although rare, malignant melanoma in children is steadily increasing and potentially lethal. Few studies have examined head and neck melanoma in the pediatric population, and even fewer have focused on the histopathologic features of melanoma within this anatomic region. To further the understanding of this entity, we examined pathology specimen from 9 subjects, under 18 years of age, with an original diagnosis of head or neck melanoma. The anatomic locations of these primary melanomas were as follows: face/nose (n=4), scalp/neck (n=4), and cutaneous ear (n=1). The cases included 7 superficial spreading melanomas, 1 possible nodular melanoma, and 1 melanoma in situ. The Breslow depth ranged from 0 to 2.9 mm (mean 1.3 mm, median 0.6 mm). Pagetoid scatter was found in eight cases. Other notable features included regression (n=5), ulceration (n=1), and associated melanocytic nevus (n=4). We did not observe any small cell variants; all 9 of our cases exhibited an epithelioid appearance. Additionally, we did not observe any melanoma-associated mortality at last follow up (mean 60.4 months, median 48 months, and range 2 to 174 months). These histopathologic features were consistent with adult-type melanoma, which is in agreement with other histopathologic studies of melanoma in children.

Abstract 12:

A CASE OF INFANTILE HUTCHINSON GILFORD PROGERIA SYNDROME

Francesca Lewis (a), Charles Darragh (a), Yekaterina Eichel (a), Kyle Radack (a), Bruce Thiers (a)
Medical University of South Carolina (a).

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare genetic condition with a reported incidence of 1 in 4-8 million births. Although HGPS is uncommon, there is much interest in the topic because of its potential implications towards understanding normal human aging. The typical onset of symptoms in HGPS occurs between 6 months and 1 year of age with skin changes and prominent scalp veins being among the earliest findings. We present a case of infantile HGPS confirmed with genetic testing positive for the Lamin A gene mutation. Our patient presented at 6 weeks of age with progressive tightness of the skin, inability to straighten the lower extremities, and prominent scalp veins, which was first noticed at 2 weeks of age. The patient was found to harbor the 1824 C>T mutation of exon 11 on the LMNA gene, diagnostic of HGPS. The patient is currently being followed by a multidisciplinary team and has been referred to the Progeria Research Foundation for treatment recommendations. Along with the case, we provide a brief discussion of the literature that has been published up to this point on HGPS.

Abstract 13:

VIRAL ASSOCIATED TRICHODYSPLASIA: A CASE IN A CARDIAC TRANSPLANT PATIENT

Bradley Greenhaw (a), Charles Darragh (a), Ross Pollack (a)
Medical University of South Carolina (a).

Viral Associated Trichodysplasia (VAT) is a scaly, erythematous, folliculocentric papular eruption that affects immunosuppressed patients with either solid organ transplants or hematolymphoid malignancies. VAT was first described in 1999 by Haycox et al, and since then fewer than 25 cases have been described in the literature. We report a case of a 26 year old African American man who presented nine months after a cardiac transplant for dilated cardiomyopathy with numerous erythematous and flesh-colored papules, some with central keratin plugs, coalescing over his entire face, along with alopecia of his eyebrows. He had similar papules scattered on his neck as well. At the time of presentation, our patient was being treated with prednisone, tacrolimus, and mycophenolate mofetil. Histopathology revealed dystrophic follicles with enlarged bulbs and trichohyaline granules, no hair shaft production, and keratin filling the follicles consistent with a diagnosis of VAT. Subsequently, our patient was treated with oral valganciclovir with modest clinical improvement. His dose ultimately had to be reduced due to agranulocytosis. This study describes the aforementioned case, provides a literature-based discussion of VAT, and explores the probable association with a newly identified polyomavirus.

Abstract 14:

KAPOSI SARCOMA IN A PREVIOUSLY UNDIAGNOSED AIDS PATIENT

Payman Kosari (a), Omar Sangueza (a), Daniel Teague (a), Joe Jorizzo (a)
Wake Forest University (a).

Kaposi sarcoma is a low-grade vascular neoplasm that has seen a resurgence in incidence since the HIV/AIDS epidemic began 30 years ago. Occurrence of lesions drastically increases as CD4 count drops. Although uncommon, Kaposi sarcoma can be a presenting sign of underlying HIV infection. We present a case of a 30 year old male that presented to Wake Forest Baptist Health with complaints of weakness, fatigue and loss of weight in the setting of multiple red-purple, indurated plaques in the oral mucosa and on the skin. Initial HIV test, 3 months ago, was negative. Repeat testing during his admission revealed that the patient was indeed HIV positive. His CD4 count was 140 cells/mL. A skin biopsy was taken and a human herpes virus-8 stain was performed confirming Kaposi sarcoma. Since the advent of highly active anti-retroviral therapy, Kaposi sarcoma has become an uncommon skin finding of HIV infection. Occasionally, it may be the presenting sign of an immunosuppressed state and must be considered in high risk individuals.

Abstract 15:

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP) INDUCED BY EXEMESTANE

Patrick Rush (a), Stefanie Hirano (a), Antoinette Hood (a)
Eastern Virginia Medical School (a).

Acute generalized exanthematous pustulosis (AGEP) is an uncommon cutaneous eruption clinically characterized by a rapid onset of numerous sterile pustules within a background of diffuse edematous erythema, typically accompanied by peripheral leukocytosis and fever. It is often precipitated by acute infection or medication administration. Our patient is an 81-year-old woman with a history of invasive ductal carcinoma and recent metastasis, who developed a fever and new skin lesions several days after starting the new aromatase inhibitor, exemestane. Histologically there were subcorneal pustular bullae with adjacent spongiosis consistent with AGEP.
As molecular techniques advance we will continue to develop and use new hormonal therapies to treat breast cancer. In our patient, there was a temporal association with exemestane and AGEP. The rash resolved with the cessation of exemestane and administration of oral steroids.

Abstract 16:

BASAL CELL CARCINOMA ARISING IN A CONGENITAL LINEAR NEVUS SEBACEOUS

Jenna O'Neill (a), Eli Sprecher (b), Joseph Jorizzo (a)
Wake Forest University (a), Tel Aviv Sourasky Medical Center (b).

A 51 year old female presented with a linear nevus sebaceous with multiple overlying pearly telangiectatic papules in a Blaschkoid distribution on the left abdomen, back, and leg, which had been present since birth. She had a history of mental impairment and hypothyroidism. She had two pearly papules biopsied by an outside physician which were consistent with basal cell carcinomas, and were subsequently excised. Biopsy of a yellow plaque within the lesion revealed nevus sebaceous and congenital nevus, while biopsy of a pearly papule revealed changes consistent with basal cell carcinoma including collections of basaloid cells with peripheral palisading and clefting between tumor and stromal cells. The extensive congenital linear nevus sebaceous, along with the history of mental impairment, are clinically consistent with Schimmelpenning syndrome. Mutations in HRAS and KRAS have recently been associated with Schimmelpenning syndrome and may predispose individuals to development of secondary tumors within nevus sebaceous. The patient is currently undergoing further genetic work-up.

Abstract 17:

VITAMIN D DEFICIENCY IN THE OUTPATIENT SETTING: AN ANALYSIS OF US NATIONALLY REPRESENTATIVE DATA

Laura Sandoval (a), Karen Huang (a), Brandy-Joe Milliron (a), Scott Davis (a), Steven Feldman (a)
Wake Forest University (a).

Background: Vitamin D deficiency is a highly researched health concern of recent years. Many countries have implemented increased vitamin D testing, despite recommendations of the Institute of Medicine and Endocrine Society.

Purpose: To characterize outpatient visits in the US that resulted in a vitamin D deficiency diagnosis.

Methods: A nationally representative survey dataset of outpatient visits from 1993-2010 was queried for visits with vitamin D deficiency diagnoses. Trends in the diagnoses over time; demographic specific diagnosis rates; and visit characteristics were identified and reported. The proportion of patients that met the Endocrine Society's criteria for testing was also determined.

Results: From 2007 to 2010, the number of visits resulting in diagnoses has rapidly increased. Asian/Pacific Islander patients were diagnosed almost 4 times as often as Caucasian patients. Females and patients ≥ 65 years of age were diagnosed 2.5 times more often than their counterparts. Visits for fatigue and metabolic disorders were most commonly associated with a diagnosis of vitamin D deficiency. Only about one half of diagnosed patients met the criteria for being tested.

Conclusion: Demographic-specific diagnosis rates support findings of the general US population. These findings also suggest that the current testing guidelines may need to be re-evaluated.

Abstract 18:

UNDERUSE OF EARLY FOLLOW-UP VISITS: A MISSED OPPORTUNITY TO IMPROVE PATIENTS' ADHERENCE

Amir Al-Dabagh (a), Scott Davis (a), Xi Tan (b), Hsien-Chang Lin (c), Rajesh Balkrishnan (b)
Wake Forest University (a), University of Michigan (b), Indiana University (c).

Background: Adherence to dermatologic treatment improves around the time of office visits. Little is known about how soon physicians schedule follow-up visit.

Purpose: To characterize the timing of first follow-up visits in US dermatologic practice.

Methods: Patients with a diagnosis of psoriasis, acne, or atopic dermatitis were identified in the 2003-2007 MarketScan Medicaid database. Factors affecting the length of time before first follow-up were assessed using a Cox proportional hazards model.

Results: Median length of time to first follow-up visit were 55 days for adults and 43 days for children with psoriasis; 62 days for adults and 103 days for children with acne; and 55 days for adults and 95 days for children in atopic dermatitis. Black and Hispanic patients were less likely than whites to receive early follow-up in psoriasis and acne, but more likely in atopic dermatitis. Dermatologists were more likely to schedule early follow-up visits than non-dermatologists.

Limitations: The database includes only Medicaid patients. The rate of non-attendance at scheduled visits could not be determined.

Conclusions: Most physicians are missing the opportunity to maximize patient adherence by scheduling early follow-up visits. Contact by email or phone may be beneficial for physicians who cannot schedule early follow-up.

Abstract 19:

DOXYCYCLINE THERAPY IN THE TREATMENT OF RETICULAR ERYTHEMATOUS MICINOSIS

Michael Graves (a), Young Kwak (a), Daniel Sheehan (a), Loretta Davis (a)
Medical College of Georgia (a).

Increasingly recognized over the years, Reticular Erythematous Mucinosis (REM) is a rare cutaneous disease that classically affects middle aged women. The lesions are typically erythematous, reticulated papules and plaques on the midline of the chest and back. Histological overlap with lupus erythematosus tumidus does exist, with both conditions showing perivascular infiltrate, mucin deposition, absence of interface change and negative direct immunofluorescence. While antimalarial drugs are considered first-line therapy for this condition, topical and systemic corticosteroids, topical calcineurin inhibitors, and ultraviolet A and B therapies have also proven helpful. We report a case of REM on the lower back of an 86 year old male. The lesions were refractory to topical steroids. Doxycycline 100 mg BID cleared the eruption within one month. Discontinuation of the doxycycline led to a flare of the same process, and re-administration of the medication resulted in further improvement. This is the first reported case of REM successfully treated with doxycycline, both initially and upon re-challenge. Doxycycline therapy should be considered for treatment of REM in patients unable to use or intolerant of antimalarial medications.

Abstract 20:

DOES SUNSCREEN USE DECREASE THE INCIDENCE OF PRIMARY CUTANEOUS MELANOMA IN CAUCASIANS: A SYSTEMATIC REVIEW

Rachel Blasiak (a), Russell Harris (a), Anthony Viera (a)
University of North Carolina at Chapel Hill (a).

To update the 2008 USPSTF recommendations on sunscreen use for primary melanoma prevention MEDLINE, the Cochrane Library, and the U.S. Government Clinical Trials website were searched for articles from 11/01/2008 to 03/08/2012. Two reviewers independently screened 264 abstracts and 75 full-text articles using predetermined inclusion and exclusion criteria. Articles were independently appraised and only good to fair quality studies were included. One good quality randomized, controlled trial and one fair quality case-control study were included in the final data synthesis. Both found a decreased risk of melanoma associated with regular sunscreen use. The RCT found a borderline significant HR of 0.50 (95% CI: 0.24 - 1.02) for all melanoma and a HR of 0.27 (95% CI: 0.08 - 0.97) for invasive melanoma. The case-control study found an adjusted OR for regular sunscreen use versus never sunscreen use of 0.44 (95% CI: 0.23 - 0.86). All other types of sunscreen use, including use during outdoor activities, thickness, amount, and reapplication were not associated with melanoma risk. Included studies did not assess harms associated with sunscreen use or melanoma associated morbidity and mortality. Overall, we bestowed a grade I recommendation on sunscreen use for the prevention of melanoma due to insufficient evidence.

Abstract 21:

SKIN CANCER KNOWLEDGE AND SKIN SELF-EXAMINATIONS IN THE HISPANIC POPULATION OF NORTH CAROLINA: THE PATIENT'S PERSPECTIVE

Carly Roman (a), Nancy Thomas (b), Aída Lugo-Somolinos (b)
Case Western Reserve University (a), University of North Carolina at Chapel Hill (b).

Our objective was to determine the percentage of Hispanics that get a skin check by a physician and perform regular SSE and explore the reasons why they may not. Patients of Hispanic descent were recruited to complete a survey regarding their knowledge of skin cancer and SSE from the Piedmont Health Services in Carrboro, NC; the University of North Carolina Dermatology Clinics, and the Hispanic advocacy group 'El Pueblo' in Raleigh, NC. Of 273 (91%) subjects who do not get a regular skin examination, 32% of the participants felt that they did not have ample time with the physician and an additional 32% reported they did not think to ask or did not know to ask for a skin exam partly because a skin examination was not the primary reason for the visit. Of 236 (78%) who do not perform a SSE yearly, the majority responded that they were not told to do so (49%) or they did not know what to look for (29%). Our results stress the importance of education to this growing population as the majority of those surveyed reported they do not get a skin check by a physician or perform a SSE.

Abstract 22:

LICHEN PLANUS COLOCALIZED WITH DEPIGMENTATION

Kristyn Morris (a), Mildred Warren (a), Antoinette Hood (a)
Eastern Virginia Medical School (a).

Lichen planus is a relatively common skin condition that accounts for approximately 1.2% of new dermatology visits. Although an autoimmune etiology is most likely involved, familial susceptibility, coexistent hepatitis C infection, and environment triggers (including drugs) have been implicated. Associated hyperpigmentation is more common than hypopigmentation, and is histologically related to pigmentary incontinence with subsequent phagocytosis by dermal melanophages. However, cases of hypopigmentation associated with lichen planus are reported in the literature as well as rare cases of depigmentation in the form of vitiligo. A unique subset of patients with vitiligo have been reported to develop subsequent lichen planus only in areas of previous depigmentation. We present a patient with acrofacial vitiligo who developed colocalized lichen planus limited to areas of depigmentation on his bilateral dorsal hands. Multiple theories have been proposed to explain this unusual clinical phenomenon however the exact pathogenesis is not understood. Understanding the interrelationship of coexisting lichen planus and vitiligo may provide insight into our understanding of the two disorders.

Abstract 23:

MALIGNANT MELANOMA IN THE GALLBLADDER – PRIMARY OR METASTASIS?

James Lin (a), Robert Pariser (b)
Eastern Virginia Medical School (a), Pariser Dermatology (b).

We report a case of a 41-year-old woman who presented with a pigmented lesion on the mid back diagnosed on biopsy as malignant melanoma with Breslow depth of 0.45 mm and clear but close margins in April 2008. She underwent excision with 1.0 cm margins in June 2008 without evidence of residual tumor. In June 2011 she presented with symptoms of cholecystitis; subsequently found to have a malignant melanoma in the gallbladder without visceral involvement. Mutational analysis of the gallbladder melanoma showed the BRAF V600E mutation. A brain MRI in June 2011 showed no abnormalities and a whole body PET scan in July 2011 showed no evidence of metastatic disease.

The distinction between primary and metastatic lesions of malignant melanoma in the gallbladder can be difficult in terms of the histopathological features alone. The lack of disease on MRI and PET suggests a primary lesion in the gallbladder. The depth of the original cutaneous melanoma on the back is of low likelihood to metastasize. In addition, the fact that the solitary melanoma of the gallbladder was found three years after excision of her melanoma on her back makes metastasis much less likely.

Abstract 24:

PSORIASIS IN THE ELDERLY

Jaclyn Hess (a), Aída Lugo-Somolinos (a)
University of North Carolina at Chapel Hill (a).

Incidence of severe outcomes in psoriasis is hard to predict and this study has aimed to determine if there are differing outcomes in older patients, over 60 years of age, compared to their more prevalent younger counterparts. The prevalence of those over the age of 60 with psoriasis is expected to increase in years to come so a better understanding of disease progression is needed. A total of 134 patients completed the anonymous survey, 41 (30.6%) of which were over the age of 60. The mean age was 49.6 years old with 61% females and 39% males. Various factors were assessed such age of onset, past medications, specifically systemic treatments, current treatments, and demographics. We found that patients over 60 were less likely to be on current systemic treatment. Also, if they were using topicals they were less likely to have previous systemic treatment, 7% had previous systemic treatment compared to 40% of their younger counterparts. The family history and location of primary outbreak in conjunction with age of onset was found to differ from previous research. This information is relevant to doctors as they try to assess disease progression and indicates the need for more extensive research.

Abstract 25:

ATYPICAL FIBROXANTHOMAS IN AN AFRICAN AMERICAN PATIENT WITH XERODERMA PIGMENTOSUM

Emily de Golian (a), Loretta Davis (a)
Medical College of Georgia (a).

A 22 year old African American male with xeroderma pigmentosum (XP) presented on two separate occasions with atypical xanthofibroma (AFX), a fibrohistiocytic tumor of the dermis. This patient embodies a particularly uncommon constellation of findings. First, atypical xanthofibroma is a rare tumor seen most commonly in elderly white males, in contrast to the young African American male described in this case. Furthermore, although xeroderma pigmentosum does occur in African American patients, the incidence is significantly lower than that seen in white patients. Finally, that these two uncommon findings coexist in the same patient is unique, as only eight cases of AFX in the setting of XP have been reported in the literature. Skin malignancies representative of XP are epidermal in origin, chiefly basal cell carcinoma, squamous cell carcinoma, and melanoma, in contrast to the dermal tumor of AFX. A review of AFX and XP supports the unusual nature of this case.

Abstract 26:

AN UNUSUAL VARIANT OF INDETERMINATE CELL HISTIOCYTOSIS

Megan Kinney (a), Lee Miller (b), Saba Ali (a), Daniel Teague (a), Vivian Hathuc (a), Omar Sangueza (a), William Huang (a)
Wake Forest University (a), Scripps Clinic (b).

A 7 year old African-American female with past medical history atopic dermatitis returned to our clinic with small pruritic bullae on her lower extremities. These were previously diagnosed as arthropod bites. This visit, skin biopsy was performed given their unusual appearance and resolution with targetoid hyperpigmented patches. Results showed an unusual variant of indeterminate cell histiocytosis positive for S-100, CD68 and negative for CD1a. Clinically, no systemic manifestations were found and routine labs were within normal limits. Indeterminate cell histiocytosis is a rare condition that clinically presents as solitary to multiple red-brown papules or nodules. Histologically, these are composed of macrophages and Langerhans cells and can manifest with different variations of the above mentioned markers. While our patient did not demonstrate systemic manifestations, findings ranging from ocular symptoms to acute myeloblastic leukemia have been documented. Treatments include light, oral immunosuppressive therapy and even pravastatin. We present this case to remind clinicians that persistent bullae in atopic dermatitis patients may not always indicate the need for a exterminator, but warrant further investigation. If a diagnosis of indeterminate cell histiocytosis is found, detailed work up to rule out systemic manifestations is prudent and many documented treatment options are available.

Abstract 27:

YOUR MANICURE AND THE RISK FOR CUTANEOUS MALIGNANCY

Lyndsay Shipp (a), Catherine Warner (a), Frederick Rueggeberg (a), Loretta Davis (a)
Medical College of Georgia (a).

Background**:** Tanning beds have come under tremendous attention for contributing to photo-aging and increasing the incidence of skin cancer. More recently, nail salon use of ultraviolet light to cure nail polish has also come under scrutiny. Ultraviolet light used in nail salons might be a risk factor for skin cancer development. (1) A mathematical modeling to estimate the skin cancer risk in clients who frequent nail salons has also been developed. (2)

Purpose**:** This study evaluated the unweighted UVA/UVB irradiance of a variety of commercial nail drying lights in commercial nail salons.

Methods**:** A UVA/UVB portable ultraviolet radiometer was used to measure unweighted irradiance values of five commercial nail drying lights. Five readings were obtained from five different lights. Values were compared using the Kruskal-Wallis ANOVA on Ranks with pair-wise multiple comparisons made by the Tukey test (alpha 0.016)

Results**:** Median irradiance values ranged from a low of 6 M/m^2 to a high of 115 M/cm^2, and were within the range previously reported as common for these types of lights (115 W/m^2)(2).

Conclusions**:** A random selection of nail drying units in commercial use was found to have a low potential for SCC development.

Abstract 28:

THE FULL SPECTRUM OF CUTANEOUS MANIFESTATIONS IN HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Mary Glover (a), Diana Murro (a), Loretta Davis (a)
Medical College of Georgia (a).

A 37-year-old Hispanic female was hospitalized for new onset congestive heart failure. Dermatology was consulted to examine the numerous yellow-brown papules and light orange plaques that were more concentrated in the intertriginous areas. The clinical findings were consistent with plane and tuberoeruptive xanthomas. Xanthelasmas and tendinous xanthomas were also found on the patient's eyelids and fingers, respectively. Lesion morphology and anatomic location led to a likely diagnosis of homozygous familial hypercholesterolemia (Frederickson type IIA hyperlipotroteinemia). Systemic findings include atherosclerosis of coronary arteries, which if left untreated can lead to myocardial infarction and congestive heart failure.

This patient reported first developing skin lesions in her early twenties but denies ever having a thorough skin examination. Her low-density lipoprotein (LDL) was found to be >280 mg/dL (normal high is 130 mg/dL), and heart catheterization revealed mutivessel coronary artery disease. If the pathognomonic cutaneous findings had been recognized earlier, the diagnosis could have been established and systemic sequelae would likely have been reduced. She is a mother of three young children, who should be closely monitored for manifestations of the heterozygous or homozygous states of familial hypercholesterolemia.

Abstract 29:

PARANEOPLASTIC LIPOATROPHY AS THE INITIAL PRESENTATION OF A CUTANEOUS MARGINAL ZONE B-CELL LYMPHOMA

Joan Paul (a), Shilpa Sawardekar (a), Kristyn Morris (a), Valerie Harvey (a)
Eastern Virginia Medical School (a).

Localized lipoatrophy is typically secondary to trauma, injections, pressure, or autoimmune connective tissue disorders. However, it can also be a rare manifestation of a cutaneous malignancy. We present the unique case of a 61-year-old female with a one-year history of lipoatrophy of the right buttock found to be secondary to cutaneous marginal zone B-cell lymphoma (CMZL). To our knowledge, there is only one other case report of CMZL presenting as localized lipoatrophy reported in the literature. This case highlights the importance of recognizing rare dermatologic manifestations of malignancies and including occult malignancy in the differential diagnosis of localized lipoatrophy.

Abstract 30:

BRISK IMPROVEMENT OF VON ZUMBUSCH GENERALIZED PUSTULAR PSORIASIS WITH INFLIXIMAB

Shilpa Sawardekar (a), Alexis Honingbaum (a), Antoinette Hood (a)
Eastern Virginia Medical School (a).

Acute generalized exanthematous pustulosis (AGEP) and generalized pustular psoriasis (GPP) are difficult to distinguish both clinically and histologically. We describe a case of an acutely sick 67-year-old female who presented to the emergency department with a generalized "burning" rash in acute renal failure. Two weeks previously, she had presented to the emergency department for evaluation of the same rash and had been discharged on an oral prednisone taper.

Her past medical history was notable for long-standing psoriasis, previously maintained (and clear) on adalimumab and topical steroids. Physical exam revealed large scaly pink patches and thin plaques, several studded with white pinpoint pustules primarily on her trunk but also including her extremities and face. Multiple laboratory abnormalities, including leukocytosis, hypocalcemia, hypoalbuminemia and elevated creatinine were also present.

Histology revealed collections of neutrophils in the stratum corneum and a dermal lymphohistiocytic infiltrate. Overall, her clinical presentation, histologic features and laboratory abnormalities are classic for the von Zumbusch variant of GPP, a type of generalized pustular psoriasis with high morbidity and mortality. She recovered rapidly with administration of infliximab.