

## BLISTERING DISEASES

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## NEIL KORMAN CONFLICTS OF INTEREST

- Director of Clinical Trials Unit at UHCMC  
- many conflicts - none relevant to this talk
- Consultant and Chair, Scientific Advisory  
Board, Immune Pharmaceuticals

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## ETIOLOGY OF BLISTERS

- Impairment or disruption of cell  
adhesion
- Cell death
- Edema (*spongiosis*)
- Trauma/physical

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## CHARACTERISTICS OF BLISTERS

### Size of lesion

- vesicle < 1cm
- bullae > 1cm

### Quality of lesion

- » flaccid
- » tense
- » Nikolsky sign

### Stage of the blister

- » early formation
- » fluid (versus serous crust)
- » EROSIONS

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## All of the Following Can Lead to Blister Formation:

- A. Viral Infection
- B. Eczematous Dermatitis
- C. Thermal Energy
- D. Radiation Injury
- E. All of the Above

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## DIFFERENTIAL DIAGNOSIS OF BLISTERS

### Infectious

- Bacterial
- Viral
- Fungal/yeast

### Non-infectious

- Hypersensitivity
- Papulosquamous disorders
- Eczematous
- **Autoimmune**

### Physical/mechanical

- Thermal injury
- Shearing forces
- Pressure
- Radiation

BROAD SCOPE OF  
DIFFERENTIALS !

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## AUTOIMMUNE BLISTERING DISEASES (AIBD'S)

- Autoantibodies target structural proteins
- Impaired epithelial adhesion
- Where is the blister located?

What is the target?




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## All of the Following are Subepidermal Blistering Diseases Except:

- A. Pemphigus Foliaceus
- B. Bullous Pemphigoid
- C. Mucous Membrane Pemphigoid
- D. Epidermolysis Bullosa Acquisita
- E. Dermatitis Herpetiformis

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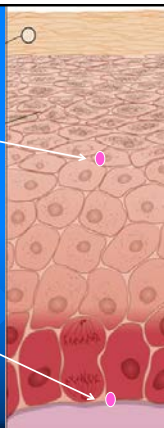
## Autoimmune Blistering Diseases

### Cell - Cell

Pemphigus vulgaris ♪  
 Pemphigus foliaceus ♪  
 Paraneoplastic pemphigus  
 Pemphigus vegetans

### Cell - Matrix

Bullous pemphigoid ♪  
 Mucous membrane pemphigoid  
 Linear IgA disease ♪  
 Epidermolysis bullosa acquisita ♪  
 Bullous SLE




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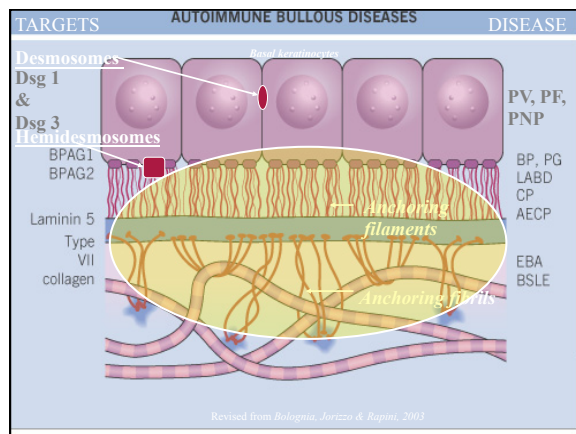
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DIAGNOSTIC TESTS FOR AIBD'S		
Tests	Specimen	Results
<b>Histopathology</b> (Hematoxylin and eosin stain)	lesional skin	location of blister, other cells that are present
<b>Immunofluorescence</b>		
•Direct (DIF)	perilesional skin	bound antibodies, complement, fibrin.
•Indirect (IIF)	sera	circulating antibodies
•Salt split skin	both	Location in the BM (roof or floor)
<b>Enzyme-linked immunosorbent assay (ELISA)</b>		Correlate w/disease activity
Desmoglein	sera	Desmoglein 1 and 3
BP Antigen	sera	BP 180 and 230

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## WHERE TO TAKE THE BIOPSY?

■ 4mm punch biopsy

H&E- Lesional  
(formaldehyde)

DIF- Perilesional  
(Michel's media)

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## Histology Alone is Sufficient to Make a Diagnosis of an AIBD

- A. True
- B. False

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## Diagnostics

- Histopathology

AND

- Direct immunofluorescence (DIF)
- Indirect immunofluorescence (IIF)
- Salt-split skin (SSS)
- Enzyme linked immunosorbent assay (ELISA)

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## IMMUNOFLUORESCENCE STUDIES ARE ESSENTIAL

- Perilesional skin or mucous membrane (normal tissue immediately adjacent to lesion) is preferred for DIF.
- Must be transported in Michel's media and MUST NEVER BE PLACED IN FORMALDEHYDE
- Accompanying serum is always helpful, but serum testing alone is difficult to interpret.
- DIF and serologies have the highest sensitivity for diagnosing BP

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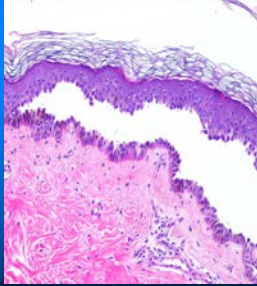
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## INTRAEPIDERMAL AIBD'S



●  
Pemphigus vulgaris  
Pemphigus foliaceus  
Pemphigus erythematosus  
Paraneoplastic pemphigus  
Pemphigus vegetans

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## All Of These Are Autoimmune Blistering Diseases Except:

- A. Pemphigus Foliaceus
- B. Dermatitis Herpetiformis
- C. Porphyria Cutanea Tarda
- D. Bullous Pemphigoid
- E. Linear IgA Bullous Disease

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## AUTOIMMUNE BLISTERING DISEASES

- Pemphigus
- Bullous Pemphigoid
- Mucous Membrane Pemphigoid
- Epidermolysis Bullosa Acquisita
- Dermatitis Herpetiformis
- Linear IgA Disease
- Pemphigoid Gestationis

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### **The Most Common Location of Pemphigus Vulgaris Lesions Is:**

- A. The palms and soles
- B. The extensor surfaces of the arms and legs
- C. The face
- D. The oral cavity
- E. The scalp

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### **INTRAEPIDERMAL AUTOIMMUNE BLISTERING DISEASES**

- The Pemphigus Family of Diseases

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### **PEMPHIGUS**

- Autoantibody mediated acantholytic blistering disease of skin and mucous membranes
- Pemphigus vulgaris is major form
- Oral lesions are the most common and are usually the presenting lesions
- Common skin sites – scalp, axilla, groin
- Mucosal dominant and muco-cutaneous disease

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### **Patients With Pemphigus Foliaceus Commonly Have:**

- A. Severe mucous membrane involvement
- B. Associated breast cancer
- C. Tense blisters on a non-erythematous base
- D. Involvement of the face, chest and back
- E. Associated scarring alopecia

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### **PEMPHIGUS FOLIACEUS**

- Much less common than pemphigus vulgaris
- Mucous membranes rarely involved
- Scaly crusted erosions – blisters rare
- Common sites – face, scalp, chest, back

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### **PARANEOPLASTIC PEMPHIGUS**

- Associated with lymphoproliferative disorders esp CLL and NHL
- Severe stomatitis with polymorphic skin eruption that can resemble many other blistering diseases such as EM, BP, MMP, LP, PV

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**Patients With Pemphigus Vulgaris  
Have All of the Following Except:**

- A. Cell surface deposits of IgG
- B. Subcorneal acantholysis on histology
- C. Circulating IgG antibodies that bind the cell surface
- D. Positive ELISA for desmoglein antibodies

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**PEMPHIGUS HISTO/  
IMMUNOPATHOLOGY**

- PV - Suprabasilar acantholysis
- PF - Subcorneal acantholysis
- PNP - Suprabasilar acantholysis and interface dermatitis
- DIF - Cell surface IgG in all patients
- IIF - Circulating IgG antibody directed against cell surface

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**PEMPHIGUS  
ELISA**

- Tests for desmoglein 1 and desmoglein 3 antibodies
- Commercially available
- Is more sensitive than IIF and has replaced IIF as the assay of choice

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## **PEMPHIGUS VULGARIS: COURSE AND PROGNOSIS**

- Untreated mortality rate of 60 – 90%
- Current mortality rate of about 5%
- Is a chronic disease

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## **CORTICOSTEROIDS**

- First used in 1940' s to treat RA
- Used in early 1950' s to treat skin diseases
- Have many strong immunosuppressive and anti-inflammatory effects
- Are cornerstone of therapy of autoimmune blistering diseases

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## **CORTICOSTEROIDS DOSING**

- Oral – initial dosing QAM with tapering to every other AM to minimize toxicity
- Intramuscular – erratic absorption
- Intravenous –for most severe disease

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### **Toxicities of Corticosteroids Include:**

- A. Osteoporosis
- B. Cataracts and Glaucoma
- C. Hypertension
- D. Diabetes
- E. All of the above

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### **CORTICOSTEROID TOXICITIES**

- |                   |                |
|-------------------|----------------|
| ■ Osteoporosis    | ■ Diabetes     |
| ■ HPA suppression | ■ Glaucoma     |
| ■ Myopathy        | ■ Peptic ulcer |
| ■ Osteonecrosis   | ■ Psychosis    |
| ■ Cataracts       | ■ Acne         |
| ■ Hypertension    | ■ Skin atrophy |

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### **CORTICOSTEROID MONITORING GUIDELINES**

- Baseline:
  - Eye exam
  - Quantiferon Gold
  - CBC
  - CMP
  - Blood Pressure
  - Hemocult
  - Bone densitometry

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### **OSTEOPOROSIS MANAGEMENT IN PTS ON CHRONIC CORTICOSTEROIDS**

- Calcium and Vitamin D supplementation
- Treatment with Bisphosphonates
- Case control study showing increased prevalence of osteoporosis in pts with pemphigus due to suboptimal monitoring and treatment

Arch Dermatol 2010;146:1126-31

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### **BISPHOSPHONATES TO PREVENT OSETOPOROSIS IN BP AND PEMPHIGUS**

- RCT of alendronate plus Ca and Vit D vs Ca and Vit D alone for 1 yr to prevent osetoporosis
- Pts with newly dx'd BP or P who would need more than 6 months of steroids were enrolled
- Bone mineral density at femoral neck and lumbar spine were significantly better in pts given alendronate compared to those who didn't

Arch Derm 2012, 148:307.

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### **Which Agent Has Not Been Studied For The Treatment for Pemphigus?**

- A. Mycophenolate Mofetil
- B. Azathioprine
- C. Rituximab
- D. Interferon
- E. Tacrolimus

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### **RANDOMIZED CONTROLLED OPEN LABEL TRIAL**

- 120 new cases of PV randomized to pred alone, pred + aza, pred + mmf, or pred + IV cyclophos
- There was lowering in mean total dose of pred needed to control pts who were given any of the adjuvants compared to pts given only pred
- Conclusion: efficacy of pred is enhanced when combined with an adjuvant and in order of decreasing efficacy they are: aza, cyc, mmf  
JAAD 2007; 57:622-8.

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### **RANDOMIZED NON-BLINDED COMPARITOR TRIAL**

- 40 pts w/PV or PF given pred + aza or pred + mmf
- 13/18 pts rxd with pred + aza achieved complete remission after mean of 74 d while 20/21 pts rxd with pred + mmf achieved complete remission after mean of 91 d (ns)
- 6/18 pts given aza and 4/21 pts given mmf had grade 3 or 4 toxicity (ns)  
Arch Derm 2006; 142:1447-54.

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### **PEMPHIGUS VULGARIS RCT PULSE STEROIDS**

- 20 newly dx'd PV pts rxd with oral dexamethasone pulses (DP) 300 mg or placebo pulses (PP) 3/mo and std rx (pred 80 mg/d tapered over 19 wks + aza 3 mg/kg)
- 8/11 DP and 9/9 PP achieved remission (ns)
- Mean time to remission 173 d vs 176 d (ns)
- Mean duration of remission 151 d vs 141 d (ns)
- Mean cum pred dose 5300 vs 4882 mg (ns)
- > 5% wt gain from baseline 8 DP vs 1 PP pt (p <.01)
- Conclusion: No advantage of adding pulse steroids

Arch Derm 2006;142:570-76.

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### **PEMPHIGUS RCT IVIg**

- 61 pts w/ PV or PF unresponsive to pred
- Placebo, 1 or 2 g/kg IVIg over 1 wk
- Endpoint – time to escape from protocol  
Unique measure taken from oncology that assesses time needed to rescue pts from study
- Time to escape from protocol prolonged in pts given 2 g/kg IVIg compared to placebo (p<.001)
- No differences in safety among three groups

JAAD 2009; 60:595-603.

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### **PEMPHIGUS RCT MYCOPHENOLATE MOFETIL**

- 94 pts with mild – moderate PV
  - Randomized to two groups - MMF 2-3 g/d and oral steroids or placebo and oral steroids
  - Primary Endpt – Percent of pts w/ absence of new lesions and prednisone dose less than 10 mg/d
  - Results – no diff in two groups in primary endpt
  - But those on MMF had faster and more durable response
- JID 2010; 130:2041-8.

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### **PEMPHIGUS RITUXIMAB STUDY**

- 21 pts with severe pemphigus (14PV, 7PF) who failed to respond, be maintained or had a contraindication to oral corticosteroids
  - One cycle of 375mg/m<sup>2</sup> weekly for 4 wks
  - 18/21 (86%) Complete remission at 3mo
  - 20/21 (95%) CR at 12 mo
  - 9/20 in CR relapsed at 19mo
  - One pt died due to sepsis
- NEJM 2007;357:545-52

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## PEMPHIGUS AND RITUXIMAB

- Retrospective cohort study 92 pts (91% PV, 9 % PF) given 1 gm Rituximab at baseline and 2 wks later with option to receive 500 mg 6 months or later
- Median time to relapse after 1<sup>st</sup> cycle – 15 months
- 39% of pts did not relapse
- Pts on concurrent adjuvant relapsed sooner
- At 2 yr f/u - 61% in CR off all Rx, 28% in CR with adjuvant Rx
- Well tolerated, no serious infections  
JAMA Derm 2014; 150:703-8.

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## PEMPHIGUS VULGARIS TACROLIMUS

- Randomized controlled non-blinded 6 month trial of 46 PV pts given either prednisolone and AZA (2.5 mg/kg) or prednisolone and Tacrolimus (0.05 mg/kg)
- All pts had same steroid taper over 10 wks
- Time to cease blistering and disease remission were same for Tacro and AZA Rxd pts
- Slightly more side effects in AZA group  
J Derm Treatment 2014, epub Feb 20

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## PEMPHIGUS TREATMENT

- Dictated by the age of the patient, degree of involvement, rate of disease progression, and subtype of pemphigus
- Patients with pemphigus foliaceus with very mild disease can occasionally be treated with topical steroids

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- Moderate pemphigus foliaceus may respond to Dapsone or Hydroxychloroquine (HCQ) alone or in combination with low dose prednisone
- Generalized pemphigus foliaceus usually requires higher dose Prednisone (~1 mg/kg) along with Dapsone & HCQ, MMF or AZA

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### **PEMPHIGUS VULGARIS TREATMENT**

- All patients with pemphigus vulgaris require systemic treatment
- Younger patients with mild-moderate disease use Prednisone 40-60 mg daily and taper to the minimum alternate day dose that controls most disease activity

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- If disease is uncontrolled with less than 20 mg Prednisone QOAM, consider adding other agents
- Dapsone may be a reasonable choice for younger patients with milder disease
- There is one study of 64 pts suggesting value of sulfasalazine and pentoxifylline as steroid sparing in PV(? Poor man's anti-TNF Rx. BJD 2009 161:313-9)

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- Older patients with moderate disease are generally treated with mycophenolate mofetil or azathioprine with Prednisone from the outset
- Patients with more severe disease may require up to 80 mg daily of Prednisone to gain control of the disease along with an immunosuppressive agent

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- As disease comes under control, Prednisone is tapered to QOAM while immunosuppressive is continued at full dosage
- When patient is clear off Prednisone, dose of immunosuppressive agent is lowered
- Immunosuppressive agent should be stopped only after negative ELISA and DIF are obtained

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- Oral disease may be the most difficult area to eradicate – topical steroids under dental mold occlusion or topical CSA can be helpful
- Patients with the most severe progressive disease consider IVIg, high dose pulse steroids, intravenous pulse cyclophosphamide, or plasmapheresis

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## **PATIENT WITH MODERATE PV**

- 40 y/o male with new onset PV involving chest, back and mouth
- Healthy with no other med problems
- How to Rx?

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## **Studies Suggest That The Best Agent To Treat Patients With Pemphigus Is:**

- A. Rituximab
- B. Mycophenolate Mofetil
- C. Dapsone
- D. Azathioprine
- E. None of the Above

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## **PEMPHIGUS: APPROACH TO TREATMENT**

- No definitive studies proving which agents are safest and most efficacious
- AZA, MMF, Rituximab are most commonly used for control of active disease with use of Rituximab becoming more common as data evolves

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## SUBEPIDERMAL BLISTERING DISEASES

- Bullous Pemphigoid
- Mucous Membrane Pemphigoid
- Epidermolysis Bullosa Acquisita
- Dermatitis Herpetiformis
- Linear IgA Disease
- Pemphigoid Gestationis

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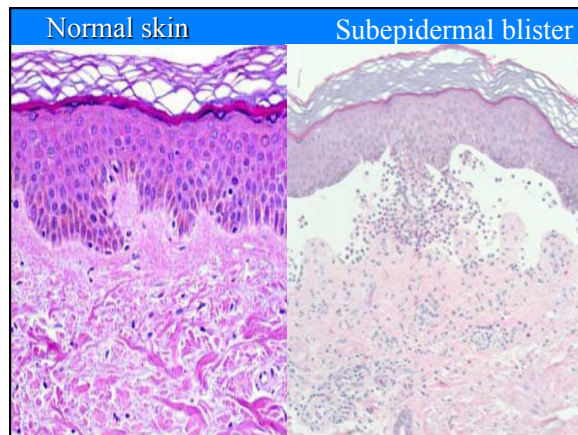
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## All of the Following Are True Re: Bullous Pemphigoid Except:

- A. The classic lesion is a tense blister
- B. Patients almost always have severe ocular disease
- C. Urticarial plaques are commonly seen
- D. It is the most common autoimmune blistering disease
- E. Peripheral eosinophilia may be present

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## BULLOUS PEMPHIGOID

- Acquired subepidermal blistering disease
- Most common autoimmune blistering disease
- Primary lesion – tense blister on normal or erythematous skin
- Often presents with urticarial plaques
- Flexural arms, legs, abdomen, groin
- Minority of pts have mucous memb disease

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## Patients With BP Have:

- A. DIF showing linear BM IgG and C3
- B. Histology subepidermal blister w/ eosinophils
- C. Circulating IgG antibodies
- D. Drug precipitated BP
- E. All of the above

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## BULLOUS PEMPHIGOID

- Some pts may have elevated serum IgE
- Pts may have peripheral eosinophilia that can correlate with severity
- May be precipitated by ultraviolet light, radiation therapy or medications (furosemide along w/several case series of gliptin class of dipeptidyl peptidase-IV inhibitors inducing BP)

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## **BULLOUS PEMPHIGOID HISTO/IMMUNOPATHOLOGY**

- Histopathology – Subepidermal blister with eosinophils
- DIF – Almost all have linear BM C3 and most have linear BM IgG (some may have linear IgE)
- IIF – Circulating IgG antibodies bind epidermal side of salt split skin

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## **BULLOUS PEMPHIGOID IIF ON SALT SPLIT HUMAN SKIN**

- 85 – 95 % of patients with BP have circulating antibodies that bind to the roof of salt split skin (SSS)
- SSS has increased sensitivity and may detect circulating antibodies that are absent when assayed on monkey esophagus or human skin

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## **BULLOUS PEMPHIGOID ELISA**

- Tests for BP 180 and 230 AB
  - Commercially available
  - Comparison of IF, ELISA and IB for dx found excellent correlation; sensitivity of 91% for DIF, 96% for IIF SSS, 96% for ELISA and 100% for IB
- Clin Exp Derm 2003; 28:651

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### Which of the Following Are True Re: the Prognosis of BP?

- A. BP is typically a benign disease
- B. BP typically lasts 1-5 years
- C. Patients with BP have a mortality rate of about 5%
- D. Patients with BP have a much better prognosis than those with pemphigus
- E. All of the above

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### BULLOUS PEMPHIGOID COURSE AND PROGNOSIS

- Usually lasts 1-5 years
- Untreated mortality rate in 5% range
- Generally less severe than pemphigus

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### RANDOMIZED NON-BLINDED COMPARATOR TRIAL

- 73 BP pts - pred + aza or pred + mmf
- 38/38 given pred + aza achieved remission after mean of 24 d while 35/35 given pred + mmf achieved remission after mean of 42 d (ns)
- 9/38 pts given aza and 6/35 pts given mmf had grade 3 or 4 toxicity (ns)
- Pts given aza had higher incidence of elevated LFT's than those given MMF ( $p < .001$ )

Arch Derm 2006; 142:1447-54

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### **BULLOUS PEMPHIGOID RCT**

- 341 pts randomized to prednisone (0.5 mg/kg for mod dis and 1 mg/kg for severe dis) or twice daily clobetasol (40 gm bid)
  - No efficacy difference between topical and systemic steroids but increased mortality in the oral steroid Rx'd pts
- NEJM 2002; 346:321-7

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### **BULLOUS PEMPHIGOID RCT**

- 312 pts - 40 gm clobetasol BID with tapering over 12 mo (std) or 20 gm BID with tapering over 4 mo (mild)
  - Std and mild regimens had same efficacy
  - Std and mild regimens had same safety
  - After adjusting for age and Karnofsky score, safety was better in mild vs std regimen
- JID 2009; 129:1681-7

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### **BULLOUS PEMPHIGOID TREATMENT**

- Dictated by the degree of involvement and the rate of disease progression
- Patients with localized disease can be treated with topical steroids
- Patients with mild generalized disease often managed with low dose Prednisone (0.5mg/kg)

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## BULLOUS PEMPHIGOID

- Treatment with Minocycline (or Doxycycline) & Niacinamide
  - Major advantage is minimal toxicity
  - Minocycline 100 mg BID (Doxycycline 100 mg BID), Niacinamide 500 mg TID
  - Most beneficial in mild disease, early in course
  - Use alone or as steroid sparing agent

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- Patients with more significant disease will need higher dose Prednisone (~1.0mg/kg)
- Patients with significant contraindications to systemic steroids may be treated with dapsone, mycophenolate mofetil, methotrexate or azathioprine
- Dapsone works best in patients with neutrophils on skin biopsy

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- Start Dapsone (after confirming normal G6PD level) 25 mg daily x 2 days to r/o idiosyncratic reaction
- Then increase to 100 mg daily
  - If no therapeutic response in 2 months, increase 25 mg per month as tolerated until disease is controlled
- Most patients will drop hematocrit – usually not a problem unless patient is older or has history of anemia or cardiovascular disease

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## BULLOUS PEMPHIGOID

- Treatment with Methotrexate
  - Given in low dosage weekly protocol similar to that used in treatment of psoriasis
  - One study showed that 10 mg or less weekly lowered the dose of Prednisone needed to control blisters after 1 month in 7 /8 patients

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- Another study of 11 patients with generalized disease revealed good control of disease when treated with 12.5 mg or less weekly, along with potent topical steroids
- Due to low dose regimen and potential for remission before reaching hepatotoxic doses, patients may not need liver biopsy

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## BULLOUS PEMPHIGOID

- Treatment with mycophenolate mofetil
  - Dose at 35-45 mg/kg
- Usual dose 2.5 - 3.5 gms per day
- Generally very well tolerated in patients with skin disease

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## BULLOUS PEMPHIGOID

- Treatment with Azathioprine
  - Dosage determined by TPMT level

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## AZATHIOPRINE METABOLISM



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## TPMT LEVELS

- 89% of normals are homozygous for high activity. (2 high alleles)
- 10.6% of normals are heterozygous. (1 high and 1 low allele)
- 0.4% of normals are homozygous for low activity. (2 low alleles)

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- Patients with very significant disease are managed with Prednisone (1.0 mg/kg) and MMF or AZA from the outset
- As disease comes under control, Prednisone is tapered to every other day while immunosuppressive is continued at full dosage
- Depending upon disease activity, steroid taper may take from several months to several years
- Only when patient is clear off Prednisone is the dose of MMF or AZA lowered

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- Major disease flare -increase steroids
- Minor flare - slow or stop the taper
- After Prednisone is stopped, AZA or MMF is continued for several months and then slowly tapered as tolerated
- Immunosuppressive agent is stopped only after negative DIF and ELISA is obtained

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**Therapies Studied to Treat BP  
Include All of the Following Except:**

- A. Dapsone
- B. Methotrexate
- C. Mycophenolate Mofetil
- D. Azathioprine
- E. Acitretin

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## **BULLOUS PEMPHIGOID**

### ■ Other treatments

- Patients with the most severe disease that is uncontrolled may be treated with pulse steroids, rituximab, intravenous immunoglobulins, or plasmapheresis

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## **OMALIZUMAB IN RX OF BULLOUS PEMPHIGOID**

- 60 – 70% of BP pts have elevated IgE levels
- 25% of pts have linear deposits of IgE at the epidermal BM on DIF
- Omalizumab is a humanized monoclonal AB that blocks binding of IgE to its receptors and is approved for treatment of asthma and chronic idiopathic urticaria

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## **OMALIZUMAB IN RX OF BULLOUS PEMPHIGOID**

- 6 typical (urticarial plaques and bullae) BP patients were treated
  - All pts had either elevated IgE or elevated eosinophil counts
  - All had steroid refractory disease and were dosed at between 300 – 400 mg q 2 – 6 wks
- JAAD 2014;71:468-74

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## OMALIZUMAB IN RX OF BULLOUS PEMPHIGOID

- 5/6 pts responded to omalizumab with no adverse reactions
- 3/6 pts responded to monotherapy
- In 2/6 pts eosinophil counts correlated with disease activity
- Omalizumab could be considered in pts with recalcitrant disease who have elevated IgE, eosinophilia or both

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## BULLOUS PEMPHIGOID: APPROACH TO TREATMENT

- Localized disease - potent topical steroids
- Mild – moderate disease - low dose prednisone
- Moderate – severe disease – adjuvant agents including dapsone, methotrexate, mycophenolate mofetil, azathioprine, rituximab IVIg, and omalizumab
- No definitive studies proving which agents are safest and most efficacious

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## Mucous Membrane Pemphigoid Patients Usually Have All of the Following Except:

- A. Eye Involvement
- B. Skin Involvement
- C. Lesions that Heal With Scarring
- D. Pediatric Presentation is the Most Common
- E. Oral Involvement

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## **MUCOUS MEMBRANE PEMPHIGOID**

- Chronic mucosal blistering dis of elderly
- Lesions heal with scarring
- Involved mucosa in order of frequency: oral, ocular, pharyngeal, nasal, laryngeal, anogenital, and esophageal
- Minority of patients also have skin disease
- Is a disease phenotype which has been divided into several distinct groups

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## **MUCOUS MEMBRANE PEMPHIGOID PHENOTYPE**

1. Patients with circulating IgG antibodies that recognize laminin-5
2. Pure ocular disease with AB to  $\beta 4$  integrin
3. Pts with mucous membrane and skin disease and IgG AB's to BP AG's
4. A heterogeneous group who have no skin disease but have oral disease with or without ocular or other mucosal disease

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## **Differences Between BP and MMP Include All But the Following:**

- A. BP usually involves skin while MMP usually involves mucous membranes
- B. Both MMP and BP have an IgA antibody response
- C. MMP lesions typically scar
- D. BP patients often have peripheral eosinophilia
- E. BP and MMP both have subepidermal blisters

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### **MUCOUS MEMBRANE PEMPHIGOID HISTO/ IMMUNOPATHOLOGY**

- Histology – subepidermal blister with inflammatory cells
- DIF – linear BMZ IgG, IgA, C3
- IIF – IgG and/or IgA antibodies which usually bind the epidermal side of split skin, but those with anti-laminin MMP bind the dermal side

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### **MUCOUS MEMBRANE PEMPHIGOID TREATMENT**

- Treatment depends upon disease extent and severity
- Mild oral disease treated with topical steroids
- More significant involvement of oral mucous membranes, skin, or genitalia are treated with Dapsone or short bursts of Prednisone

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### **MUCOUS MEMBRANE PEMPHIGOID**

- Treatment of Oral Mucous Membrane Disease
  - Mild disease topical or intralesional steroids
  - Topical viscous lidocaine to reduce pain
  - Use acrylic mold to apply topical steroids to gingiva

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- Topical cyclosporine (100mg/5cc swish and spit or squeeze contents of capsule on the involved mucosa)
- Patients with more significant disease are treated with Dapsone
- Patients with the worst oral disease and severe gingivitis causing loosening of teeth - treat w/ Prednisone (~1.0 mg/kg) and Dapsone

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## **MUCOUS MEMBRANE PEMPHIGOID**

- Treatment of Ocular Disease
  - Ocular disease is most serious type of mucous membrane pemphigoid
  - These patients require aggressive treatment to prevent destruction of the meibomian and mucous glands which lubricate the eye
  - All patients must be treated systemically

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- Some believe that Prednisone and Dapsone is reasonable approach to patients with moderate disease with progression to Azathioprine, or MMF in progressive disease and to Cyclophosphamide for those with the worst disease
- Others insist that all patients be treated with Prednisone and Cyclophosphamide (1.0 mg/kg or higher until the white blood cell count equals 3.0 - 4.0)

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**Toxicities of Cyclophosphamide  
Include All of the Following Except:**

- A. Nephrotoxicity
- B. Bladder Cancer
- C. Hypertension
- D. Elevated Triglycerides
- E. Gout

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»Prednisone is tapered over 6 months and  
Cyclophosphamide is continued for  
18-24 months

»About 75% of these patients experience  
long-term remission

- Risks of this treatment include bone  
marrow suppression, hemorrhagic cystitis,  
increased risk of infection and increased  
risk of lymphoma and bladder cancer
- Intravenous pulse Cyclophosphamide  
along with Prednisone has been reported  
to be beneficial but with lowered risks

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**MUCOUS MEMBRANE  
PEMPHIGOID**

- Treatment of Other Involved Sites
  - Patients with skin or genital involvement  
may be managed with topical, or in more  
severe cases, systemic steroids
  - Patients with esophageal or laryngotracheal  
involvement should be treated aggressively  
with Prednisone and Cyclophosphamide to  
prevent major life-threatening complications  
of asphyxiation and esophageal stenosis

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- Patients with severe esophageal stenosis may require esophageal dilatation
- Patients with mucous membrane pemphigoid may develop severe scarring requiring surgical intervention
  - » This must not occur until the disease is under good control because more inflammation with further scarring will otherwise ensue

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- If surgical procedures are absolutely necessary, such as lysing conjunctiva adhesions, dilating the esophagus, or resecting laryngeal stenosis, then the level of immunosuppression should be increased for at least 3 weeks before and after the procedure

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## **MUCOUS MEMBRANE PEMPHIGOID**

- Other treatments
- IVIg – high dose 2–3g/kg given QOWK
- Rituximab

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### **MMP RX WITH RITUXIMAB**

- 25 refractory MMP pts
- 1-2 cycles of 375mg/m<sup>2</sup> x 4wk
- 3mo: 17/25 CR; 5/8 achieved CR after 2nd cycle
- 10/22 (45%) who had CR of ocular & extraocular lesions relapsed at 4mo
- SAEs: 3 infections, 2/3 died  
Arch Derm 2011;147:843-9

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### **Patients with Pemphigoid Gestationis Have All of the Following Except:**

- Is an autoimmune blistering disease of pregnancy
- Most commonly occurs in the 2<sup>nd</sup> – 3<sup>rd</sup> trimester
- Is typically associated with preeclampsia
- Presents with urticarial papules and plaques
- May flare peri-partum

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### **HERPES GESTATIONIS AKA PEMPHIGOID GESTATIONIS**

- Autoimmune blistering disease of pregnancy
- Most commonly occurs in 2<sup>nd</sup> – 3<sup>rd</sup> trimester
- Pruritic urticarial plaques in periumbilical area
- Progresses to vesicles and blisters and can spread to entire abdomen and extremities
- Can flare peri-partum
- Can flare with OCP's, menstruation and pregnancy

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## PEMPHIGOID GESTATIONIS

- Increased risk of small for gestational age baby
- Comanage these pts with high risk obstetrician
- Small chance of PG in babies born to mothers with PG due to transplacental transfer of antibodies
- These resolve within 6 months of age due destruction of maternal antibodies
- May be associated with Graves disease

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## PEMPHIGOID GESTATIONIS DIAGNOSIS

- Histology - papillary edema and subepidermal blister with eosinophils
- DIF – linear C3 at the epidermal BM
- IIF – usually not helpful
- ELISA for BP 180 is positive

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## PEMPHIGOID GESTATIONIS TREATMENT

- Mild disease can be treated with topical steroids and antihistamines
- For more severe disease oral steroids are treatment of choice
- Steroid sparing agents usually not used due to potential risk to baby but if necessary discuss risk/benefit with obstetrician

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## EPIDERMOLYSIS BULLOSA ACQUISITA

- Rare acquired autoimmune subepidermal blistering disease
- Has clinical features similar to either the genetic dis dystrophic epidermolysis bullosa known as non-inflammatory form or similar to bullous pemphigoid known as the inflammatory form

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## Patients with EBA Have Which of the Following?

- Hyperkalemia
- An eosinophil predominance on histology
- A neutrophil predominance on histology
- A genetic tendency to develop this disease
- Are easily treated with standard agents

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## EPIDERMOLYSIS BULLOSA ACQUISITA

- Clinical features include: skin fragility, blisters, erosions, scars, milia, and nail loss
- All pts have skin bound and or circulating IgG antibodies directed against type VII collagen

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## **EBA ASSOCIATIONS**

- Occurs more commonly in pts with ulcerative colitis
- Closely related to bullous eruption of SLE

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## **EBA DIAGNOSIS**

- Histo – subepidermal blister with no inflammation or with neutrophils
- DIF – linear deposits of IgG at epidermal basement membrane
- IIF on salt split human skin – antibodies binding to the dermal side of salt split skin
- ELISA – antibodies directed against type VII collagen – now commercially available

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## **EBA TREATMENT**

- May be most difficult to treat of all the autoimmune blistering diseases
- Due to rarity of disease - no controlled studies
- Therapies include colchicine, dapsone, systemic corticosteroids, and all of the immunosuppressive agents.
- Role for cyclosporine
- Role for IVIg

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## **EBA RITUXIMAB**

- 9 case studies since Sadler et al (BJD 2007)
- CR after sev mo in 6/9 (67%)
- PR remaining pts
- One case series of 5 pts (Le Roux-Villet, C, Arch Derm 2011)  
CR all pts  
4 relapsed at median 9 mo

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## **BULLOUS SYSTEMIC LUPUS ERYTHEMATOSUS**

- Autoantibodies to type VII collagen
- African American, 2nd-3rd decade, F>M
- Sun exposed (head and neck), axilla, mucosal
- Resembles DH or BP, NOT like discoid lupus
- Typically vesicles

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## **DIAGNOSTIC CRITERIA BSLE**

Clinical criteria for SLE  
Vesiculobullous eruption  
Subepidermal blister with neutrophil stuffing of papillae  
DIF – linear granular deposits of IgG, IgM, IgA, C3 and Fibrinogen at BM  
IIF - circulating IgG AB' s binding base of salt split skin

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## DERMATITIS HERPETIFORMIS

- Pruritic vesiculobullous autoimmune disease
- Associated with gluten sensitive enteropathy
- Typically occurs in middle age
- Severe pruritus
- Presents with erosions usually no intact vesicles
- Symmetric involvement of elbows, knees buttocks and scalp

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## DERMATITIS HERPETIFORMIS HISTO/IMMUNOPATH

- Subepidermal cleft with neutrophil stuffing of dermal papillae
- DIF - granular IgA in dermal papillae
- Routine IIF is negative
- ELISA for epidermal transglutaminase is positive

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## DERMATITIS HERPETIFORMIS ASSOCIATIONS

- Gluten sensitive enteropathy – asymptomatic
  - Typically does not require GI evaluation
- Autoimmune thyroid disease and type 1 diabetes
- Increased risk of lymphoma of the bowel that is decreased in pts on gluten free diet

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**Rituximab Is Used to Treat All of the Following Except:**

- Pemphigus Vulgaris
- Dermatitis Herpetiformis
- Bullous Pemphigoid
- Mucous Membrane Pemphigoid
- Epidermolysis Bullosa Acquisita

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**DERMATITIS HERPETIFORMIS TREATMENT**

- Dapsone is treatment of choice
- Dapsone dosed at 50 – 300 mg daily
- Patients may have flares requiring short term increases in dapsone dose
- Some patients may also need prednisone
- Gluten free diet very valuable

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**True or False?**

- Linear IgA Disease is thought to be a similar entity to chronic bullous disease of childhood
- Linear IgA disease often responds well to treatment with dapsone
- Some patients with LIGA disease can have ocular disease that resemble ocular MMP

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## LINEAR IGA DISEASE

- Autoimmune blistering dis mediated by IgA
- Occurs in all age groups
- Chronic bullous disease of childhood appears to be same disease as LIGA of adulthood
- Typically presents with tense blisters sometimes in a ring
- Occasional pts will have ocular involvement that can be indistinguishable from ocular MMP

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## LINEAR IGA DISEASE HISTO/IMMUNOPATH

- Histology – subepidermal blister with neutrophils
- DIF – linear deposits of IgA at epidermal BM
- IIF – circulating IgA antibody that typically binds to the roof of SSS
- ELISA – Currently unavailable

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## LINEAR IGA DISEASE TREATMENT

- Dapsone is treatment of choice
- Some patients require addition of oral steroids
- Patients with most severe disease will require addition of steroid sparing agents such as mycophenolate mofetil or azathioprine
- IVIg and rituximab may also be helpful for pts with the most recalcitrant disease

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