Outpatient Consultations in Complex Medical Dermatology
Selected Aspects: 2016

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Conflict of Interest

Advisory Boards/Honoraria

Amgen
Leo Pharmaceuticals
Quote from an anonymous patient:
“What I am told on the first visit is patient education – on the second an excuse.”
Possibilities for a patient who presents with a complex medical dermatosis and systemic signs and symptoms:

1. Clinicopathologic diagnosis of dermatosis integrates all findings eg. Sarcoidosis – skin, eye, lungs, etc

2. Clinicopathologic diagnosis reveals a reactive dermatosis – communication with internist or pediatrician will outline underlying medical conditions eg. Vasculitis

3. No direct relationship – eg. Scabies/Fibromyalgia
Patients wishes to know from the internet whether they need x or y therapy for their presumptive diagnosis. Instead it is important to not let the patient “drive” for their own benefit.
Step 1. – Clinicopathologic diagnosis- Caution influence of therapy on biopsy and clinical appearance

Step 2. – Assess the extent (internal manifestations of disease)

Step 3. – Assess for etiology

Step 4. - Therapeutic ladder
Cutaneous Vasculitis

Key Features

- Cutaneous signs of vasculitis are a reflection of the size of the vessels involved
- Vasculitis can be limited to the small vessels of the skin or it can be a sign of life-threatening internal organ involvement
- The clinical diagnosis of cutaneous vasculitis requires histopathologic confirmation and multiple biopsies may be required
<table>
<thead>
<tr>
<th>Caliber of the predominantly affected vessel</th>
<th>Classification</th>
<th>Subclassification or etiologies</th>
<th>Morphology of cutaneous lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>Cutaneous small vessel vasculitis (CSVV)</td>
<td>Henoch–Schönlein purpura, Acute hemorrhagic edema of infancy, Urticarial vasculitis, Erythema elevatum diutinum, Secondary causes of CSVV (see Table 24.3): – Drug exposure – Infections – Malignancies, most often hematologic</td>
<td>Palpable purpura (most common), Petechiae, Macular purpura, Urticarial papules, Vesicles, Pustules, Targetoid papules and plaques</td>
</tr>
<tr>
<td>Small and medium-sized (&quot;mixed&quot;)</td>
<td>Cryoglobulinemia, ANCA-associated</td>
<td>Types II and III, Microscopic polyangiitis, Wegener’s granulomatosis, Churg–Strauss syndrome, Secondary causes: Infections, Inflammatory disorders (e.g. AI-CTD)</td>
<td>Petechiae, Palpable purpura, Livedo racemosa, Retiform purpura, Ulcers, Subcutaneous nodules, Digital necrosis</td>
</tr>
<tr>
<td>Medium-sized</td>
<td>Polymyositis nodosa (PAN)</td>
<td>Classic (systemic) PAN, Cutaneous PAN</td>
<td>Livedo racemosa, Retiform purpura, Ulcers, Subcutaneous nodules, Digital necrosis</td>
</tr>
<tr>
<td>Large*</td>
<td>Temporal arteritis</td>
<td>Early – erythematous or cyanotic skin, alopecia, purpura, tender nodules on frontotemporal scalp, Late – Ulceration and/or gangrene of frontotemporal scalp or tongue</td>
<td>Erythematous subcutaneous nodules +/- ulceration, pyoderma gangrenosum-like lesions on the extremities (lower &gt; upper), May have evidence of small and/or medium-sized vessel vasculitis</td>
</tr>
</tbody>
</table>

*Cutaneous manifestations are rare.

Table 24.1 Cutaneous vasculitis classification scheme. AI-CTD, autoimmune connective tissue diseases.

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Vasculitis: 2016
Classification Problems:
The example of the ACR Criteria

- Age at disease onset > 16 years
- Medication at disease onset
- Palpable purpura
- Biopsy including arteriole and venule with histologic change showing granulocytes in perivascular or extravascular location

Three criteria are required
SPECIAL ARTICLE

2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

Classification Advances

2012 Update of Chapel Hill Consensus Classification

1. Introduction of New Terms
   a) Granulomatosis with polyangiitis
   b) IgA vasculitis

2. Categories of Variable vasculitis

3. Categories of Secondary Vasculitis

ACR/EULAR – study to develop diagnostic and classification criteria

Input (including from dermatologists) at 2013 ACR meeting
Fig. 24.1 Pathogenesis of cutaneous vasculitis – immune complex-versus ANCA-mediated. A In immune complex-mediated vasculitis, circulating antigens (e.g., infectious agents, medications, neoplasms) induce antibody formation. Binding of antibodies to circulating antigens creates immune complexes. Immune complex deposition within post-capillary venules activates complement and subsequently leads to an increase in adhesion molecule expression on the endothelium. Complement split products (C3a and C5a) induce mast cell degranulation and neutrophil chemotaxis. Mast cell degranulation leads to increased vascular dilation and permeability, enhancing immune complex deposition and leukocyte tethering to endothelium. Increased adhesion between inflammatory cells (especially neutrophils) and the endothelium is mediated by elevated expression of selectins (E-selectin, P-selectin) and members of the immunoglobulin superfamily (ICAM-1, VCAM-1, PECAM-1) on endothelial cells in concert with the upregulation of their corresponding ligands and receptors/adhesion molecules on leukocytes (e.g., P-selectin glycoprotein ligand-1, LFA-1, Mac-1). Neutrophil release proteolytic enzymes (such as collagenases and elastases) and free oxygen radicals that damage the vessel wall. In addition, formation of the membrane attack complex (C5-C9) on the endothelium leads to the activation of the clotting cascade and the release of cytokines and growth factors with ensuing thrombosis, inflammation and angiogenesis. B In ANCA-mediated vasculitis, intracellular proteins from neutrophils (e.g., proteinase 3 [PR3], myeloperoxidase [MPO]) become expressed on the cell surface. After formation of ANCA that recognize these antigens, binding of the autoantibodies to neutrophils leads to increased neutrophil adhesion to vessel walls and subsequent cellular activation. Neutrophils then release reactive oxygen species and other toxic mediators that result in vessel wall damage (see A). Because the vessel damage in ANCA-positive vasculitides is directly mediated by neutrophils rather than by immune complexes, they are referred to as “papul-immune” vasculitides.
Today’s Focus
Cutaneous Small Vessel Vasculitis

Key Features
- Palpable purpura, urticarial lesions, hemorrhagic macules or vesicles
- Lesions favor the lower extremities (especially the ankles), dependent areas or pressure points
- Only involves small vessels (primarily postcapillary venules)
Cutaneous Small Vessel Vasculitis

Key Features (Cont.)

- Histopathologically, leukocytoclastic vasculitis is seen
- Extracutaneous involvement occurs, but it is uncommon and usually mild.
Vasculitis: 2016
Clinical Features
Cutaneous Small Vessel Vasculitis
Fig. 24.2 Cutaneous small vessel vasculitis. A Classic presentation of purpuric papules on the distal lower extremities; a few lesions have become vesicular. B Early lesions may be pink papules. C Central necrosis with formation of hemorrhagic crusts. D Digital infarcts.
A, Courtesy, Kalman Watsky, MD. C, Courtesy, Frank Samarin, MD.
Fig 24.3 Clinical variants of cutaneous small vessel vasculitis. A Targetoid appearance that can resemble erythema multiforme. B Hemorrhagic crusts in annular configuration. C Lesions limited to the upper extremities – an unusual distribution pattern.
Vasculitis: 2016
Cutaneous Small Vessel Vasculitis
Histopathologic Features

- Endothelial cell swelling
- Neutrophilic invasion of vessel walls
- Leukocytoclasia (neutrophilic nuclear karyorrhexis)
- Extravasation of erythrocytes
- Fibrinoid necrosis of vessel walls
Cutaneous Small Vessel Vasculitis

Selected Subtypes

- IgA Vasculitis – Henoch-Schönlein Purpura
- Acute hemorrhagic edema of infancy
- Urticarial vasculitis
- Erythema elevatum diutinum
- Cryoglobulinemic vasculitis
- Cutaneous small vessel vasculitis with various autoimmune connective tissue disease
Cutaneous Small Vessel Vasculitis: Evaluation for Systemic Involvement

- Utilize the primary care internist or pediatrician
- Where are immuno reactants most likely to deposit?
  - Kidney
  - Pleura/perocardium
  - GI tract
  - Central or Peripheral nervous system
  - Joint Synovia
  - Retina
  - Adrenal Glands
  - etc
Etiology

Work with a colleague, generally in internal medicine, to perform sequential evaluations that include history and physical examination not just laboratory tests.

Categories include:

**Drugs:** (be careful: association does not prove causation!)

**Infections:** Viral, bacterial, Deep fungal, AFB, other

**Disease with immune complexes:** Autoimmune connective tissue dieases, other autoimmune, inflammatory bowel disease, autoimmune liver disease, Behcet’s disease, malignancy especially myelodysplastic diseases. (Curth’s postulates)
Fig. 24.5 Etiologies of cutaneous small vessel vasculitis.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>First-line treatment</th>
<th>Evidence levels</th>
<th>Second-line treatment</th>
<th>Evidence levels</th>
<th>Third-line treatment</th>
<th>Evidence levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous small vessel vasculitis</td>
<td>Discontinue (incurred) drugs</td>
<td>2&lt;sup&gt;++&lt;/sup&gt;</td>
<td>Colchicine (6-8 mg/bid-tid)</td>
<td>3</td>
<td>Aza (2 mg/kg/day)</td>
<td>3</td>
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<tr>
<td></td>
<td>Supportive care</td>
<td></td>
<td>Dapsone (150-200 mg/day)</td>
<td></td>
<td>MTX</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Antimalarials</td>
<td>3&lt;sup&gt;++&lt;/sup&gt;</td>
<td>Hydroxychloroquine</td>
<td>3</td>
<td>Prednisolone</td>
<td>3</td>
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<td>3</td>
<td>Methotrexate</td>
<td>3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CS</td>
<td></td>
<td>Myc</td>
<td>3</td>
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<td></td>
<td></td>
<td></td>
<td>Aza + CS</td>
<td>2</td>
<td>CSA</td>
<td>3</td>
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<td></td>
<td></td>
<td></td>
<td>CYC + CS</td>
<td>3</td>
<td>PEX</td>
<td>3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Antimalarials</td>
<td>3</td>
<td>Factor XII</td>
<td>3</td>
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<tr>
<td>Acute hemorrhagic Rhinos of infancy</td>
<td>Supportive care</td>
<td>3&lt;sup&gt;++&lt;/sup&gt;</td>
<td>Colchicine</td>
<td>3</td>
<td>Methotrexate</td>
<td>3</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Antimalarials</td>
<td>3</td>
<td>Dapsone (100-200 mg/day)</td>
<td>3</td>
<td>Prednisolone</td>
<td>3</td>
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<tr>
<td></td>
<td>Inmunosuppressants</td>
<td></td>
<td>Hydroxychloroquine</td>
<td>3</td>
<td>Methotrexate</td>
<td>3</td>
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<tr>
<td></td>
<td>Dapsone (500-1000 mg/day)</td>
<td>2&lt;sup&gt;++&lt;/sup&gt;</td>
<td>Aza</td>
<td>3</td>
<td>Prednisolone</td>
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<tr>
<td>Erythema elevatum diutum</td>
<td>NSAIDs</td>
<td>3</td>
<td>CS</td>
<td>3</td>
<td>Methotrexate</td>
<td>3</td>
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<td></td>
<td>Intermittent CS</td>
<td></td>
<td>Colchicine</td>
<td>3</td>
<td>Prednisolone</td>
<td>3</td>
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<tr>
<td></td>
<td>Intermittent CS</td>
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<td>Hydroxychloroquine</td>
<td>3</td>
<td>Methotrexate</td>
<td>3</td>
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<tr>
<td>Crocoglobatemic Vasculitis (HCV)</td>
<td>IFN + ribavirin</td>
<td>3</td>
<td>CS + CYC</td>
<td>3&lt;sup&gt;++&lt;/sup&gt;</td>
<td>Methotrexate</td>
<td>3</td>
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<tr>
<td>Curaneous polyarthritis nodosa</td>
<td>Treat underlying infections</td>
<td>3</td>
<td>MTX (7.5-15 mg/qd)</td>
<td>3</td>
<td>Prednisonolone</td>
<td>3</td>
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<tr>
<td></td>
<td>Discontinue (incurred) drugs</td>
<td></td>
<td>Dapsone + sulfasulfone</td>
<td>3</td>
<td>Methotrexate</td>
<td>3</td>
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<tr>
<td>Classic polyarthritis nodosa (CIDP)</td>
<td>NSIDs</td>
<td>2</td>
<td>CS + CYC</td>
<td>2&lt;sup&gt;++&lt;/sup&gt;</td>
<td>Methotrexate</td>
<td>3</td>
</tr>
<tr>
<td>Clonid (polyarthritis CDA)</td>
<td>CS + PLEX + IFN+Adenovirus</td>
<td>2</td>
<td>CS + CYC</td>
<td>3</td>
<td>Methotrexate</td>
<td>3</td>
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<tr>
<td>Microscopic polyangiitis</td>
<td>CS + CYC</td>
<td>3</td>
<td>CS + Ritasynab + CYC</td>
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<td>Methotrexate</td>
<td>3</td>
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<td>Wegener's granulomatosis (to induce</td>
<td>CS + MTX</td>
<td>2</td>
<td>TMP-SMX (CS)</td>
<td>2</td>
<td>Methotrexate</td>
<td>3</td>
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<td>remission in limited disease)</td>
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<td></td>
<td>Methotrexate</td>
<td>3</td>
</tr>
<tr>
<td>Wegener's granulomatosis (to induce</td>
<td>CS + CYC + Ritasynab + CYC</td>
<td>1</td>
<td>CS + CYC + PEX</td>
<td>1</td>
<td>Methotrexate</td>
<td>3</td>
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<tr>
<td>remission in generalized disease)</td>
<td></td>
<td></td>
<td>CS + CYC + PEX</td>
<td></td>
<td>Methotrexate</td>
<td>3</td>
</tr>
<tr>
<td>Wegener's granulomatosis (to maintain</td>
<td>CS + Aza + MTX</td>
<td>3</td>
<td>CS + CYC + PEX</td>
<td>1</td>
<td>Methotrexate</td>
<td>3</td>
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<td>remission)</td>
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<td>Methotrexate</td>
<td>3</td>
</tr>
<tr>
<td>Wegener's granulomatosis (to maintain</td>
<td>CS + CYC</td>
<td>3</td>
<td>CS + CYC + PEX</td>
<td>1</td>
<td>Methotrexate</td>
<td>3</td>
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<td>remission)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methotrexate</td>
<td>3</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>CS + MTX</td>
<td>3</td>
<td>CS + CYC + PEX</td>
<td>1</td>
<td>Methotrexate</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 24.10 Therapeutic ladder for patients with vasculitis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. ACA, aminocaproic acid; Aza, azathioprine; CS, corticosteroids; CYC, cyclophosphamide; CSA, cyclosporine; HBV, hepatitis B virus; HCV, hepatitis C virus; IFN, interferon; IVig, intravenous immunoglobulin; MTX, methotrexate; MYC, mycophenolate mofetil; NSAI ds, nonsteroidal anti-inflammatory drugs; PEX, plasmapheresis; TMP-SMX, trimethoprim-sulphamethoxazole. Key references for treatment are summarized. References cited in this table (*) are available in the online content.

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Vasculitis: Update 2016
Therapeutic Ladder:
Non-ulcerative Cutaneous Lesions

- No Therapy
- Topical therapies
  (access to site of pathology)
- Gradient Support Hose
- Antibiotics
- Pentoxifylline
- Colchicine
- Dapsone/Sulfapyridine
- Combination Colchicine/Dapsone
Vasculitis: Update 2016 Therapeutic Ladder: Ulcerative Cutaneous Lesions or Minimal Systemic Disease

- Various topical (from corticosteroids to dapsone to metronidazole to imiquimod)
- Weekly Pulse Methotrexate
- Prednisone with slow taper
- Thalidomide
Vasculitis Update: 2016
Therapeutic Ladder - More Severe Diseases

- Prednisone alone or in combination
- Pulse Prednisone
- Azathioprine
- Cyclophosphamide; pulse or daily
- Mycophenolate mofetil
- Chlorambucil
- Cyclosporine
- TNF alpha inhibitors
- Leflunomide
- Rituximab (Mostly SLE patients with vasculitis)
- Countless treatments aimed at underlying diseases
Urticaria

An inflammatory dermatosis resulting from vasodilatation, increased vascular permeability, and extravasation of protein and fluids. Individual lesions, by definition, last less than 24 hours.
Definitions

- Urticaria (hives) - reaction in the superficial dermis; lesions last less than 24 hours
- Urticarial reaction - similar, but lesions last more than 24 hours
- Angioedema - reaction in the submucosa, deep dermis, and subcutaneous tissue
- Acute urticaria - less than 6 weeks
- Chronic urticaria - more than 6 weeks
A Personal Classification of Urticarial Reactions

- IgE-dependent urticaria and angioedema
  - Specific antigen identified
  - Physical urticarias
- Non-IgE dependent urticaria angioedema
  - Direct mast cell effects
  - Arachidonic acid pathway effects
- Angioedema related to complement
  - Hereditary
  - Acquired
- Urticarial reactions probably related to immune complexes
  - Urticarial vasculitis
  - Serum sickness-like reactions
- Idiopathic
IgE-Dependent Urticaria: Some examples of implicated causes

- Infections: Bacterial (eg. Dental abscess, sinusitis)
  Fungal (eg. Candida, dermatophyte)
  Viral (eg. Hepatitis B)
  Other
- Infestations: Helminths, protozoa, other
- Drugs and Chemicals: Penicillin, sulfonamides, other
- Foods: Eggs, nuts, chocolate, shellfish, other
- Inhalents: Pollens, animal dander, other
- Systemic Disease: Lymphomas, collagen vascular diseases, other
Fig. 19.7 Causes of acute urticaria.
(Data from Zuberbier, 1996.)
Fig. 19.8 Causes of chronic urticaria. Autoimmune represents those patients with functional autoantibodies against FcεRI or the Fc portion of IgE.

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IgE-Dependent Urticaria

- Rarely proven by RAST, Scratch testing, or other methods
- Suggestive evidence for reagins (IgE or IgG4) in urticaria
Urticaria
Clinical Lesions: Urticarial Wheal
Urticaria

Clinical Lesions: Generalized Wheals
Urticaria
Clinical Lesions: Angioedema
<table>
<thead>
<tr>
<th>Urticaria due to mechanical stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermographism</td>
</tr>
<tr>
<td>• Immediate</td>
</tr>
<tr>
<td>• Simple</td>
</tr>
<tr>
<td>• Symptomatic</td>
</tr>
<tr>
<td>• Delayed</td>
</tr>
<tr>
<td>Delayed pressure urticaria</td>
</tr>
<tr>
<td>Vibratory angioedema</td>
</tr>
<tr>
<td>• Inherited</td>
</tr>
<tr>
<td>• Acquired</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urticaria due to temperature changes and stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat and stress</td>
</tr>
<tr>
<td>• Cholinergic urticaria</td>
</tr>
<tr>
<td>• Localized heat contact urticaria</td>
</tr>
<tr>
<td>Stress</td>
</tr>
<tr>
<td>• Adrenergic urticaria</td>
</tr>
<tr>
<td>Cold</td>
</tr>
<tr>
<td>• Cold contact urticaria</td>
</tr>
<tr>
<td>• Primary</td>
</tr>
<tr>
<td>• Secondary (cryoglobulins, cryofibrinogen)</td>
</tr>
<tr>
<td>• Atypical cold urticaria, e.g. reflex, familial cold urticaria</td>
</tr>
<tr>
<td>Exercise-induced urticaria</td>
</tr>
<tr>
<td>• Exercise-induced anaphylaxis</td>
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<tr>
<td>• Food- and exercise-induced anaphylaxis</td>
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<table>
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<tr>
<th>Solar urticaria</th>
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<table>
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<tr>
<th>Aquagenic urticaria</th>
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</table>

*Rare variants are not shown here for simplicity (see text).*

**Table 19.3 Classification of physical urticarias by the eliciting stimulus.**

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Symptomatic Dermatographism: Diagnosis

- Stroke skin of back with fingernail or even use dermographometer
- Observe for wheal formation
  - Onset - Minutes
  - Duration - 2 to 3 hours
- Delayed form exists
Urticaria
Clinical Lesions: Symptomatic dermatographism
Cholinergic Urticaria Diagnosis

- Exercise testing (Does not exclude exercise-induced anaphylaxis-Caution!)
- Hot bath testing - Immerse 1/2 of patient at 43°C (Raise oral temperature 1° to 1.5°C)
  **Best Test**
- Intradermal injections (methacholine, etc.)
  **Unreliable**
- Observe for wheal formation
  Onset - 2-20 minutes
  Duration - 30 minutes to 1 hour
Cold Contact Urticaria - Diagnosis

- Exclude secondary cold urticaria
- Ice filled copper beaker with thermometer
  Vary exposure
- Ice cube test (use plastic gloves)
- Cold immersion - One arm in water 8° - 10°C for 5 minutes
- Cold air - Expose 1/2 the patient to a cold room for 20-30 minutes
  Extreme caution
- Observe for wheal formation
  Onset - 2-5 minutes
  Duration - 1-2 hours
Urticaria

Clinical Lesions: Cold Contact Urticaria
Other Physical Urticarias

- **Pressure Urticaria** - 8kg/4cm weight to thigh
  Onset - 3-12 hours
  Duration - 8-24 hours

- **Heat Urticaria** - Cooper beaker with 50-55°C water
  Onset - 2-5 minutes
  Duration - 1 hour
Other Physical Urticarias - Continued

- Aquagenic Urticaria - Water compress with thermometer to maintain temperature at 35-36°C for 30 minutes
  Onset - Several minutes to 30 minutes
  Duration - 30 minutes

- Vibratory Angioedema - Vibrating mixer against skin
  Onset - 2-5 minutes
  Duration - 1 hour
Non-IgE-Dependent Urticaria: Some agents which effect mast cells directly

- Radiocontrast material
- Opiates (eg. Morphine)
- Polymyxin B
- Curare and d-tubocurarine
Non-IgE-Dependent Urticaria: Arachidonic acid pathway modification

- Non-steroidal anti-inflammatory drugs
  (not sodium salicylate)
- Up to 10% of asthma patients and 50% of urticaria patients are intolerant to aspirin
- Possible associated intolerance to azodyes
  (eg. Tartrazine and benzoate preservatives)
- Mechanism related to increased lipoxigenase products after cyclooxygenase blockade
Angioedema Related to Complement

- **Hereditary:** Dominant inheritance with functional or absolute deficiency of the inhibitor of the first component of complement (C1-normal, family members may be abnormal)

- **Acquired:** Lymphoma patients (C1-reduced, family members normal)
Urticarial Reactions Probably Related To Circulating Immune Complexes

- Urticarial vasculitis
- Serum sickness-like reactions

Patients often have fever, urticarial lesions lasting more than 24 hours, lymphadenopathy, myalgias, arthralgias or arthritis, and possibly proteinuria, elevated liver function tests, leukocytosis, and high sedimentation rate.
Urticaria

Clinical Lesions: Urticarial vasculitis
Urticaria
Clinical Lesions: Urticarial serum sickness - like reaction
Anti-FcεRI Autoantibodies Mediate Release and Account for About One-Quarter of Cases of Chronic Urticaria

- Circulating histamine - releasing factors
- Autoantibodies against the IgE high-affinity receptor, FcεRI in sera
- 163 patients with CIU versus healthy controls
- Histamine release from mast cells and basophils
- 1/4 of patients had antibodies which could do this

Chronic Idiopathic Urticaria: Newer Data on Autoimmunity

- Autologous serum skin test
- Subgroup with autoimmune thyroid disease
- Basophil activating IgG autoantibodies
MAST CELL DEGRANULATING STIMULI

- Allergen
- IgE
- Anti-FceRI
- Anti-IgE
- Substance P
- Stem cell factor
- C5a
- Codeine
MEDIATORS RELEASED BY DERMAL MAST CELL DEGRANULATION

- Release of pre-formed mediators
  - Proteases (e.g., tryptase)
  - Heparin
  - Histamine

- Synthesis of newly-formed mediators
  - Prostaglandin D₂
  - Leukotrienes C₄, D₄, E₄
  - Platelet-activating factor
  - Cytokines (e.g., IL-3, -4, -5, -6, -8, -13, GM-CSF, TNF-α)
IgE ANTIBODY BINDING TO FcεRI
Fig. 19.17 Approach to the diagnosis of chronic urticaria.
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My Evaluation of Patients with Chronic Idiopathic Urticaria

- Complete history and physical examination by Primary Care Physician (PCP)
- Screening laboratory tests and follow up of positives by PCP (eg. if eosinophilia then stool for ova and parasites and other complete evaluation)
- Review medications and avoid all non-steroidal antiinflammatory drugs (due to increased lipoxygenase products)
- Discuss anaphylactoid symptoms and signs and give appropriate prophylaxis (eg. Epipen8 or Anakit7 if needed)
Circle lesions - biopsy if circled lesion lasts more than 24 hours (not urticaria by definition therefore, exclude urticarial vasculitis, etc.)

Consider (3) day rice and water elimination diet

Review prognosis and limited chance for total cure

Consider activated charcoal therapy
My Treatment Approach for Patients with Chronic Idiopathic Urticaria

- Avoid (and/or taper to zero if already receiving) systemic corticosteroids
- Recognize impact of disease on quality of life
- Review that antihistamine will only flatten lesions and reduce pruritus not “eliminate the red” as corticosteroids do
- Combine several antihistamines from different classes with different sedating potential and $H_1$ and $H_2$ blocking effects taking half life into effect
My Treatment Approach for Patients with Chronic Idiopathic Urticaria (continued)

- For example **combine** one or two from first category:

  Non-sedating or low sedating antihistamine
  Levocetirizine 5mg  1x/day

  or
  Loratidine or 10mg  1x/day

  or
  180mg  1x/day

  With
  Doxepin 10 – 75 mg at bedtime
Consider adding other classes or montelukast, stonozolol 2mg bid medication (eg. Terbutaline sulfate, nifedipine, colchicine, dapsone, zafirlukast-leukotriene inhibitor)

Consider (realizing risks and frequent lack of success) immunosuppressive approach for patients with very refractory disease as follows:

- Psoralen ultraviolet A (PUVA)
- Methotrexate (weekly low dose)
- Azathioprine daily
- Cyclosporine (short course 3-4 months only)
- Pulse cyclophosphamide
- Oral Tacrolimus
- IVIG
- Omalizumab (Xolair – anti IgE) 150 or 300 mg SQ q weeks (150mg/site max)
Fig. 19.21 Management of ordinary and physical chronic urticarias.
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<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Chemical family</th>
<th>Half-life (hours)</th>
<th>Daily adult dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic (sedating)</td>
<td>Chlorpheniramine (1)</td>
<td>Alkylamine</td>
<td>25</td>
<td>4 mg tid (up to 12 mg at night)</td>
</tr>
<tr>
<td></td>
<td>Hydroxyzine (1)</td>
<td>Piperazine</td>
<td>20</td>
<td>10–25 mg tid (up to 75 mg at night)</td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine (2)</td>
<td>Ethanolamine</td>
<td>4</td>
<td>10–25 mg at night</td>
</tr>
<tr>
<td></td>
<td>Doxepin** (1)</td>
<td>Tricyclic antidepressant</td>
<td>17</td>
<td>10–50 mg at night</td>
</tr>
<tr>
<td>Second-generation</td>
<td>Acrivastine (1)</td>
<td>Alkylamine</td>
<td>2–4</td>
<td>8 mg tid</td>
</tr>
<tr>
<td></td>
<td>Cetirizine*** (1)</td>
<td>Piperazine</td>
<td>7–11</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Loratadine (1)</td>
<td>Piperidine</td>
<td>8–11</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Mizolastine (1)</td>
<td>Piperidine</td>
<td>13</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Newer second-generation</td>
<td>Desloratadine (1)</td>
<td>Piperidine</td>
<td>19–35</td>
<td>5 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Fexofenadine (1)</td>
<td>Piperidine</td>
<td>17</td>
<td>180 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Levocetirizine (1)</td>
<td>Piperazine</td>
<td>7–10</td>
<td>5 mg once daily</td>
</tr>
<tr>
<td>H₂ antagonists†</td>
<td>Cimetidine (1)</td>
<td></td>
<td>2</td>
<td>400 mg bid</td>
</tr>
<tr>
<td></td>
<td>Ranitidine (2)</td>
<td></td>
<td>2–3</td>
<td>150 mg bid</td>
</tr>
</tbody>
</table>

*Current prescribing manuals should be consulted for details on doses in children.
**Possesses potent H₁ and H₂ antihistaminic properties.
***The active metabolite of hydroxyzine.

Table 19.4 Antihistamines for chronic urticaria. A short-acting classic antihistamine may be added at night to a daily second-generation antihistamine, with or without the addition of an H2 antagonist for maximal antihistamine blockade. †Used in combination with H1 antagonists. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

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<table>
<thead>
<tr>
<th>Generic name</th>
<th>Drug class</th>
<th>Route</th>
<th>Dose</th>
<th>Special indication/associated diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone (2)</td>
<td>Corticosteroid</td>
<td>Oral</td>
<td>0.5 mg/kg qd</td>
<td>Severe exacerbations (days only)</td>
</tr>
<tr>
<td>Epinephrine (2)</td>
<td>Sympathomimetic</td>
<td>sc, im (self-administered)</td>
<td>300–500 µg</td>
<td>Angioedema of throat/anaphylaxis</td>
</tr>
<tr>
<td>Montelukast (3)</td>
<td>Leukotriene receptor antagonist</td>
<td>Oral</td>
<td>10 mg qd</td>
<td>Aspirin-sensitive urticaria</td>
</tr>
<tr>
<td>Thyroxine (2)</td>
<td>Thyroid hormone</td>
<td>Oral</td>
<td>50–150 µg qd</td>
<td>Autoimmune thyroid disease</td>
</tr>
<tr>
<td>Nifedipine (1)</td>
<td>Calcium antagonist</td>
<td>Oral</td>
<td>10–40 mg modified-release qd</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Colchicine (3)</td>
<td>Neutrophil inhibitor</td>
<td>Oral</td>
<td>0.6–1.8 mg qd</td>
<td>Neutrophilic infiltrates in lesional biopsy specimens</td>
</tr>
<tr>
<td>Sulfasalazine (3)</td>
<td>Aminosalicylates</td>
<td>Oral</td>
<td>2–4 g qd</td>
<td>Delayed pressure urticaria</td>
</tr>
</tbody>
</table>

Table 19.5 Some second-line medications for chronic or physical urticaria. Current prescribing manuals should be consulted for details on dose, drug interactions and contraindications for individual patients. The stated doses represent guidelines only. Key to evidence-based support (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

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Bullous Pemphigoid

Key Features

- Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease; it predominantly affects the elderly
- It is usually a chronic disease, with spontaneous exacerbations and remissions, which maybe accompanied by significant morbidity
- BP is associated with tissue-bound and circulating autoantibodies directed against BP antigen 180 (BP180, BPAG2 or type XVII collagen) and BP antigen 230 (BP230 or BPAG1e), components of junctional adhesion complexes called hemidesmosomes that promote dermal-epidermal cohesion
Bullous Pemphigoid

Key Features (Cont.)

- The spectrum of clinical presentations is extremely broad. Characteristically, BP is an intensely pruritic eruption with widespread blister formation. In early stages, or in atypical variants of the disease, only excoriated, eczematous or urticarial lesions (either localized or generalized) are present.

- Diagnosis relies on immunopathologic examinations, particularly direct and indirect immunofluorescence microscopy as well as anti-BP180/BP230 ELISAs.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Target antigen(s)</th>
<th>Mol. wt. [kDa]</th>
<th>Morphologic structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullous pemphigoid (BP)</td>
<td>BP180/BPAG2/collagen XVII</td>
<td>180</td>
<td>Hemidesmosomal plaque/anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>BP230/BPAG1e</td>
<td>230</td>
<td>Hemidesmosomal plaque</td>
</tr>
<tr>
<td>Gestational pemphigoid</td>
<td>BP180/BPAG2/collagen XVII</td>
<td>180</td>
<td>Hemidesmosomal plaque/anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>BP230/BPAG1e</td>
<td>230</td>
<td>Hemidesmosomal plaque</td>
</tr>
<tr>
<td>Mucous membrane (cicatrical) pemphigoid</td>
<td>BP180/BPAG2/collagen XVII</td>
<td>180</td>
<td>Hemidesmosomal plaque/anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>BP230/BPAG1e</td>
<td>230</td>
<td>Hemidesmosomal plaque</td>
</tr>
<tr>
<td></td>
<td>Laminin 5 (332; α3β4γ2 epiligrin)</td>
<td>165, 140, 105</td>
<td>Anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>Laminin 6 (311; α3β4γ1)</td>
<td>165, 220, 200</td>
<td>Anchoring filaments/extracellular matrix</td>
</tr>
<tr>
<td></td>
<td>Integrin β4 subunit</td>
<td>200</td>
<td>Hemidesmosomal plaque/anchoring filaments</td>
</tr>
<tr>
<td>Linear IgA bullous dermatosis (LABD)</td>
<td>LAD antigen†</td>
<td>97/120</td>
<td>Anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>BP180/BPAG2/collagen XVII</td>
<td>180</td>
<td>Hemidesmosomal plaque/anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>BP230/BPAG1e†</td>
<td>230</td>
<td>Hemidesmosomal plaque</td>
</tr>
<tr>
<td></td>
<td>Type VII collagen†</td>
<td>290/145</td>
<td>Anchoring fibrils</td>
</tr>
<tr>
<td>Epidermolysis bullosa acquisita</td>
<td>Type VII collagen†</td>
<td>290/145</td>
<td>Anchoring fibrils</td>
</tr>
<tr>
<td>Anti-p200 pemphigoid</td>
<td>Laminin γ-1 chain</td>
<td>200 kDa</td>
<td>Extracellular matrix</td>
</tr>
<tr>
<td>Bullous systemic lupus erythematosus</td>
<td>Type VII collagen†</td>
<td>290/145</td>
<td>Anchoring fibrils</td>
</tr>
</tbody>
</table>

†Detectable in a subset of patients

‡Binding to laminin 6 (331) depends on the presence of cross-reactive autoantibodies directed against the α-chain of laminin 5 (332).

§Reactivity with the cytoplasmic domain of the β4 subunit of the α6β4 integrin described in a subset of patients with ocular cicatrical pemphigoid.

Table 30.1 Major autoantigens of subepidermal autoimmune-mediated blistering diseases. Not an exhaustive list. In the course of these diseases, it is possible to detect autoantibodies directed against additional antigens, the significance of which remains to be established. In certain cases, a so-called “internmolecular epitope spreading” phenomenon is thought to occur.
Fig. 30.2 Bullous pemphigoid – bullous presentation. Classic presentation with multiple tense bullae arising on normal and erythematous skin. Several of the bullae have ruptured, leaving circular erosions.
Fig. 30.3 Bullous pemphigoid – urticarial (and bullous) presentation. (A) Pink urticarial papules and plaques as well as tense bullae containing serous fluid. (B) Firm annular urticarial plaques.
Fig. 30.4 Bullous pemphigoid – eczematous presentation. (A), (B) Large pink eczematous plaques on the trunk and upper extremities.
Fig. 30.5 Bullous pemphigoid – unusual clinical variants.
Grouped vesicles and bullae on the palms (A) and toes (B) that can resemble pompholyx (dyshidrosiform pemphigoid). (C) Vegetating plaque in the inguinal crease (pemphigoid vegetans). (D) Toxic epidermal necrolysis-like lesions with large erosions.
Fig. 30.6  Childhood bullous pemphigoid.  (A) Generalized tense bullae and crusted erosions.  (B) Localized vulvar involvement (vulvar childhood pemphigoid).
Fig. 30.7 Bullous pemphigoid localized to a psoriatic plaque. No obvious trigger was detected, as the patient was not receiving phototherapy. Courtesy, Jean L. Bolognia, MD
Fig. 30.8 Urticarial phase of bullous pemphigoid – histologic features. Eosinophils are present within the dermis as well as the epidermis (eosinophilic spongiosis). Some of the eosinophils have lined up at the dermal-epidermal junction, a typical finding in the urticarial stage of BP. Courtesy, Lorenzo Cerroni, MD
Fig. 30.9 Bullous pemphigoid – histologic features. Subepidermal blister which contains fibrin, eosinophils and mononuclear cells (see insert). Courtesy Lorenzo Cerroni, MD
<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Design</th>
<th>Group 1:</th>
<th>Group 2:</th>
<th>Response</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roujeau et al. (1984)</td>
<td>Randomized</td>
<td>Prednisolone (0.3 mg/kg/day)</td>
<td>Prednisolone + 6 plasma exchanges</td>
<td>Total and daily corticosteroid doses needed for disease control lower in group 2</td>
<td>Low prednisolone dose</td>
</tr>
<tr>
<td>Morel &amp; Guillaume (1984)</td>
<td>multicenter</td>
<td>Prednisone (0.75 mg/kg/day)</td>
<td>Prednisone (1.25 mg/kg/day)</td>
<td>At day 51, remission in group 1 (33%) and group 2 (59%) not significantly different</td>
<td>Trend for a better response in group 2</td>
</tr>
<tr>
<td>Guillot et al. (1986)</td>
<td>Non-randomized</td>
<td>Prednisolone alone</td>
<td>Prednisolone plus long-term plasma exchange</td>
<td>At month 6, relapse rate and total corticosteroid doses lower in group 2</td>
<td>Risk of severe side effects in group 2</td>
</tr>
<tr>
<td>Dreno et al. (1993)</td>
<td>Randomized</td>
<td>Methylprednisolone (1–1.5mg/kg/day)</td>
<td>Prednisolone (1–1.5mg/kg/day)</td>
<td>At day 10, no difference in response except for better decline of pruritus in group 1</td>
<td>Analysis of early response only</td>
</tr>
<tr>
<td>Guillaume et al. (1993)</td>
<td>Randomized</td>
<td>Prednisolone (1 mg/kg/day) alone</td>
<td>Prednisolone and acetylprine (100–150 mg/day)</td>
<td>At month 6, no significant difference in remission rate between group 1 (42%), group 2 (59%) and group 3 (29%)</td>
<td>More complications in group 2. No adjustment of doses of acetylprine based on TPMT levels</td>
</tr>
<tr>
<td>Fleronson et al. (1994)</td>
<td>Randomized</td>
<td>Nicotinamide (1.5 g/day) plus tetracycline (2 g/day)</td>
<td>Prednisone (40–80mg/day)</td>
<td>At month 1, no difference in response, but fewer side effects in group 1</td>
<td>Low number of studied patients. High drop-out rate</td>
</tr>
<tr>
<td>Joly et al. (2002)</td>
<td>Randomized</td>
<td>Topical dlobetasol propionate</td>
<td>Prednisone 0.5–1mg/kg/day</td>
<td>At week 3, control rates better in group 1</td>
<td>At year 1, topical therapy is associated with a significantly reduced mortality and complication rate</td>
</tr>
<tr>
<td>Debsert et al. (2007)</td>
<td>Randomized</td>
<td>Methylprednisolone (0.5 mg/kg) with acetylprine (2 mg/kg)</td>
<td>Methylprednisolone (0.5 mg/kg) with mycophenolate mofetil (2 g daily)</td>
<td>Disease control similar in the two groups</td>
<td>In group 1, higher incidence and severity of liver toxicity. Trend for faster disease control and less total cumulative doses of steroids in group 1. No adjustment of doses of acetylprine based on TPMT levels</td>
</tr>
<tr>
<td>Joly et al. (2009)</td>
<td>Randomized</td>
<td>Topical dlobetasol propionate standard regimen for 12 months (40 g daily as starting dose)</td>
<td>Topical dlobetasol propionate, mild regimen for 6 months (10–30 g daily as starting dose)</td>
<td>Time to achieve disease control of BP similar in both groups. At 1 year, trend for higher relapse rate in patients with moderate BP treated with mild regimen</td>
<td>In moderate BP treated with mild regimen, decrease in the risk of death/ side effects. Lower cumulative dose of dlobetasol in mild regimen</td>
</tr>
</tbody>
</table>

Table 30.3 Survey of controlled trials for the treatment of patients with bullous pemphigoid. TPMT, thiopurine methyltransferase.
Tips for Bullous Pemphigoid

1. Antibacterial body washes/Bleach baths
2. Topical triamcinolone 0.1% cream 3:1 in Silvadene cream
3. Weekly methotrexate corrected for age/creatinine
4. Lower dose prednisone
5. 2 year program

Pemphigus Vulgaris

Key features

- Pemphigus is a group of autoimmune blistering diseases of the skin and mucous membranes that is characterized by:
  - histologically, intraepidermal blisters due to the loss of cell-cell adhesion of keratinocytes
  - immunopathologically, the finding of in vivo bound and circulating IgG autoantibodies directed against the cell surface of keratinocytes
- Pemphigus is divided into three major forms: pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus
Pemphigus Vulgaris

Key features (cont.)

- The functional inhibition of desmogleins, which play an important role in cell-cell adhesion of keratinocytes, by IgG autoantibodies results in blister formation.

- Patients with pemphigus vulgaris and pemphigus foliaceus have IgG autoantibodies against desmoglein 3 and desmoglein 1, respectively, while patients with paraneoplastic pemphigus have IgG autoantibodies against plakin molecules in addition to autoantibodies against desmogleins.

- IgA autoantibodies directed against the keratinocyte cell surface define IgA pemphigus, the pathophysiology of which is yet to be clarified.
<table>
<thead>
<tr>
<th>Classification of Pemphigus</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pemphigus vulgaris</td>
</tr>
<tr>
<td>• Pemphigus vegetans</td>
</tr>
<tr>
<td>• Pemphigus foliaceus</td>
</tr>
<tr>
<td>• Pemphigus erythematosus: localized</td>
</tr>
<tr>
<td>• Fogo selvagem: endemic</td>
</tr>
<tr>
<td>• Herpetiform pemphigus</td>
</tr>
<tr>
<td>• Drug-induced pemphigus</td>
</tr>
<tr>
<td>• Paraneoplastic pemphigus</td>
</tr>
<tr>
<td>• IgA pemphigus</td>
</tr>
</tbody>
</table>

Table 29.1 Classification of pemphigus.
Indirect immunofluorescence of pemphigus sera with normal human epidermis as a substrate. The hallmark of pemphigus is the finding of IgG autoantibodies directed against the cell surface of keratinocytes.

A. Pemphigus vulgaris sera containing anti-desmoglein 3 (anti-Dsg3) IgG alone stain the cell surfaces in the lower epidermis.

B. Pemphigus vulgaris sera containing both anti-Dsg3 IgG and anti-Dsg1 IgG stain the cell surfaces throughout the epidermis.

C. Pemphigus foliaceus sera, which contain only anti-Dsg1 IgG, stain the cell surfaces throughout the epidermis, but more intensely in the superficial layers.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantibodies</th>
<th>Antigens</th>
<th>MW (kDa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus vulgaris</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal-dominant type</td>
<td>IgG</td>
<td>Desmoglein 3</td>
<td>130</td>
</tr>
<tr>
<td>Mucocutaneous type</td>
<td>IgG</td>
<td>Desmoglein 3</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desmoglein 1</td>
<td>160</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>IgG</td>
<td>Desmoglein 1</td>
<td>160</td>
</tr>
<tr>
<td>Paraneoplastic pemphigus</td>
<td>IgG</td>
<td>Desmoglein 3</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desmoglein 1</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plectin</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desmoplakin I</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desmoplakin II</td>
<td>210</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BPAG1</td>
<td>230</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enveloplakin</td>
<td>210</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Periplakin</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A2ML1</td>
<td>170</td>
</tr>
<tr>
<td>Drug-Induced pemphigus</td>
<td>IgG</td>
<td>Desmoglein 3</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desmoglein 1</td>
<td>160</td>
</tr>
<tr>
<td>IgA pemphigus†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcorneal pustular dermatosis</td>
<td>IgA</td>
<td>Desmocollin 1</td>
<td>110/100</td>
</tr>
<tr>
<td>type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraepidermal neutrophilic type</td>
<td>IgA</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

*Members of plakin family.
†A subset of patients have IgA autoantibodies against Dsg1 or Dsg3.

Table 29.2 Target antigens in pemphigus. A2ML1, alpha-2-macroglobulin-like-1 protease inhibitor; BPAG1, bullous pemphigoid antigen 1.
Fig. 29.5 Pemphigus vulgaris. A, B. Essentially all patients develop painful oral mucosal erosions, with the most common sites being the buccal and palatine mucosae.

C. Flaccid blisters and an erosion due to rupture of a bulla.

B-D, Courtesy, Louis A Fragola, Jr, MD
**Fig. 29.5 Pemphigus vulgaris**

**D.** The dyshidrosiform variant is uncommon.

**E.** In a severe case, a large area of the back is affected, leading to a loss of body fluids and secondary bacterial infections.

_B-D, Courtesy, Louis A Fagola, Jr, MD_  
_E, Courtesy, Department of Dermatology, Hamamatsu University School of Medicine_
**THERAPEUTIC LADDER FOR PEMPHIGUS VULGARIS**

### STANDARD TREATMENT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral prednisone</td>
<td>1.0 mg/kg/day as an initial dose (usually 60 mg/day) (1)</td>
</tr>
</tbody>
</table>

### AGGRESSIVE TREATMENT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressive agents in combination with oral prednisone:</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2–4 mg/kg/day (usually 100 to 300 mg/day) (1)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>2–3 g/day (2)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1–3 mg/kg/day (usually 50 to 200 mg/day) (2)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>5 mg/kg/day (2)</td>
</tr>
<tr>
<td>Pulse methylprednisolone</td>
<td>1 g/day over a period of 2–3 hours for 3–5 consecutive days (2)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>7.5–20 mg/week (3)</td>
</tr>
<tr>
<td>Pulse cyclophosphamide</td>
<td>50 mg/kg/day × 4 days (3)</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>1–2 times per week, at the onset (2)</td>
</tr>
<tr>
<td>High-dose IV Ig</td>
<td>400 mg/kg/day for 5 consecutive days (1); may need to be repeated</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m² once weekly for 4 weeks (2)</td>
</tr>
<tr>
<td>Extracorporeal photopheresis</td>
<td>2 days per month (3)</td>
</tr>
</tbody>
</table>

### TOPICAL TREATMENT

- Topical corticosteroids (1), especially Class I to localized persistent sites
- Topical antibiotics (2)
- Topical immunomodulators (e.g. cyclosporine, tacrolimus) (3)

Table 29.5 Therapeutic ladder for pemphigus vulgaris. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.
Tips for Pemphigus Vulgaris

- Waterpick
- Manage Candida acutely with fluconazole and chronically with daily clotrimazole troches
- CREST whitening (dilute hydrogen peroxide)
- 1mg tacrolimus capsule (open & dissolve in ½ liter of water – swish and spit for 2 minutes (Ortonne)
- Topical and/or intralesional corticosteroids
- Choose: Rituximab versus Prednisone and Mycophenolate

Lupus Erythematosus Update: 2016

Introduction

- Dermatologists are uniquely qualified to understand clinicopathologic aspects of lupus erythematosus especially from the mucocutaneous vantage point.
- Avoid Lupus/Skin/Antimalarials rut
- Match the therapy to the presumed pathogenesis of lesions
Fig. 41.1 Pathogenesis of lupus erythematosus. A In photosensitive cutaneous LE, ultraviolet radiation (UVA and UVB) triggers cytokine and chemokine production, initiating an immune response. B A lichenoid tissue reaction is the endpoint of a complex cascade that includes activation of dendritic cells, release of interferon (IFN), production of chemokines, and activation of T cells. BMZ, basement membrane zone; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; CXCR, chemokine (C-X-C motif) receptor; HMGBl, high-mobility group box 1; IL, interleukin; ICAM, intercellular adhesion molecule; pDC, plasmacytoid dendritic cell; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

Lupus Erythematosus: Approach

- Evaluate dermatologic lesions based on clinicopathologic features
- Work with a colleague in Pediatrics or Internal Medicine to evaluate relevant internal involvement
- Classify patient appropriately as to subset
- Construct a therapeutic ladder
Lupus Erythematosus Update: 2016

Therapeutic Classification

- Vascular reactions in SLE
- Lesions characterized by a lymphocytic infiltrate at the DE junction
  - Discoid lesions (CCLE or SLE)
  - Subacute lesions (SCLE)
  - Poikiloderma (SLE)
- Special lesions
  - Lupus panniculitis
  - Vesiculobullous lesions
  - Tumid lesions
Lupus Erythematosus Update: 2016

Vascular Reactions

- Probably immune complex-mediated (CIC)
  - Cutaneous small vessel vasculitis
  - Larger vessel vasculitis
  - Other forms
    - Urticarial vasculitis
    - Other serum sickness-like lesions

- Uncertain mechanism
  - Erythemas
  - Erythema multiforme-like lesions
  - Livedo reticularis
  - Other vascular reactions
Lupus Erythematosus
Cutaneous Small Vessel Vasculitis
Lupus Erythematosus
Larger Vessel Vasculitis
Lupus Erythematosus Update: 2016

Interface Lesions

- Discoid lesions (scarring)
  - CCLE
  - SLE
- Subacute cutaneous lesions (nonscarring)
  - Annular-polycyclic
  - Psoriasiform
- Poikiloderma - SLE
Lupus Erythematosus
Spectrum of Interface Lesions: Discoid Lesion
Lupus Erythematosus Update: 2016
CCLE vs. SLE

- Biopsy confirmation
- Complete cutaneous examination to exclude:
  - Nailfold telangiectasias
  - Vasculitic lesions
  - Poikiloderma
  - SCLE annular lesions
Lupus Erythematosus Update: 2016
CCLE vs. SLE

- Complete history and physical examination aimed at ARA criteria for SLE
- Screening laboratory tests aimed at ARA criteria to include at least:
  - ANA profile
  - Urinalysis
  - Complete blood count and platelets
  - SMAC
- Role of direct immunofluorescence
<table>
<thead>
<tr>
<th>Autoantibodies And Their Clinical Associations 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-dsDNA</strong></td>
</tr>
<tr>
<td><strong>Anti-Sm</strong></td>
</tr>
<tr>
<td><strong>Anti-Ro</strong></td>
</tr>
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<tr>
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<tr>
<td>Autoantibodies</td>
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<td>--------------------------------------</td>
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<tr>
<td>Anti-La</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Anti-RNP</td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Antiribosomal P</td>
</tr>
</tbody>
</table>
Autoantibodies And Their Clinical Associations 2016 continued...

- Antiphospholipid
  - Recurrent spontaneous abortions
  - Arterial and venous thrombosis
  - Thrombocytopenia
Lupus Erythematosus: Current ACR Criteria (Undergoing Revision)

- Malar rash
- Discoid lupus
- Photosensitivity
- Oral ulcers
- Arthritis
- Proteinuria > 0.5g/day or cellular casts
- Seizures or psychosis
- Pleuritis or pericarditis
- Hemolytic anemia or leukopenia or lymphopenia or thrombocytopenia
- Antibody to DNA or Sm antigen
- Positive FANA

Refer to: Arthr Rheum 2012;64:2677-2686
For Systemic Lupus; International Collaborating Clinics Classification Criteria
Lupus Erythematosus
Spectrum of Interface Lesions: Subacute Lesions
Lupus Erythematosus
Spectrum of Interface Lesions: Poikiloderma
Drug Induced LE (Often SCLE)

- Thiazide diuretics
- NSAIDS (remember Aleve/naproxen)
- Calcium channel blockers
- Antifungals – terbinafine, griseofulvin
- Beta blockers
- ACE inhibitors – eg. Captopril
- TNF alpha inhibitors
- Misc – ranitidine, taxofere, cinnarizine, stations, procainamide, penicillamine, phenytoin, interferons alpha & beta
Lupus Erythematous Update: 2016
Interface Lesions: Therapeutic Ladder

- Mild and/or localized disease
  - Sunscreens (High SPF with UVA protection) (2)
  - Topical corticosteroids (2)
  - Superpotent topical corticosteroids (2)
  - Intralesional corticosteroids (2)
  - Topical immunomodulators
    - eg. Tacrolimus +/- Keratolytics (2)
  - Hydroxychloroquine 200mg bid (1)
  - Above plus Quinacrine 100mg qd (2)
Lupus Erythematosus: Update 2016
Therapeutic Ladder
Extensive/Persistent Cutaneous Disease

- Oral Retinoids (2)
- Dapsone/Sulfapyridine (2)
- Chlofazimine (3)
- Methotrexate (3)
- Thalidomide (2)
- Auranofin (3)
- Azathioprine (2)
- Mycophenolate
Lupus Erythematosus: Update 2016
Therapeutic Ladder Systemic Disease

- Prednisone (1)
- Azathioprine (1)
- Mycophenolate (1)
- Leflunomide (2)
- Cyclophosphamide (1)
- IVIG (2)
- Cyclosporine (1)
- Rituximab (2)
- Belimumab (Anti B-LyS) (1)
- Tofacitinib (JAK inhibitor)
Lupus Erythematosus: Update 2016
Therapeutic Ladder
Systemic Disease Experimental Therapies

- Mesenchymal stem cells
- Nanoparticle-based drug delivery
- Sirukumab (anti-Il-6)
- Tocilizumab (anti-Il-6 receptor)
- Eculizumab (anti-C5)
- Many others strategies
Lupus Erythematosus Update: 2016
Special Lesions: Therapeutic Ladder

- Lupus Panniculitis
  - Antimalarials (2)
  - Other
Lupus Erythematosus Update: 2016
Special Lesions: Therapeutic Ladder

- Vesiculobullous Lesions (EBA relationship)
  - Dapsone (2)
  - Azathioprine (3)
  - Mycophenolate mofetil (3)
Why is this important for dermatologists?

- Serious, treatable, multisystem disease
- Prognosis and therapy different from lupus erythematosus
- Malignancy association in adults
- Diagnosis is commonly (maybe even usually) missed
Dermatomyositis: 2016

Reasons we dermatologists might miss the diagnosis

- Miss poikiloderma - diagnose as psoriasis - risk of phototherapy
- Note poikiloderma but miss photodistribution and nail fold changes - diagnose as cutaneous T-cell lymphoma
- Note poikiloderma and photodistribution - diagnose as lupus erythematosus - ANA and skin biopsy specimen may seem to support the misdiagnosis
Dermatomyositis Update: 2016 - Diagnosis
Bohan and Peters, 1975

- Clinical signs and symptoms of proximal extensor muscle weakness
- Elevations of muscle enzymes (e.g. CPK, Aldolase)
- EMG changes of myositis
- Typical muscle histologic changes (infiltrate, necrosis, fibrosis, phagocytosis, regeneration)
- Typical cutaneous eruption

New criteria are evolving
Role of MRI debated
Juvenile Dermatomyositis: 2016

- 8-22% of all DM/PM
- Higher incidence of vasculitis
- Early studies: 1/3 died, 1/3 crippled, 1/3 remission
- Recent studies: Low mortality (vasculitis with GI hemorrhage)
- Calcinosis cutis more common
Dermatomyositis: 2016
Malignancy Association

- No increase in incidence of neoplasia in children
- 5-11 fold increase in neoplasia in adults
  (PM: 2-3%; DM: 15-20%)
- Particularly lung, ovary, breast, stomach
- Usually DM antedates tumor by 1-2 years
- Drop off in malignancy after two years - Large Danish study
- “Directed” evaluation – repeated at intervals
Dermatomyositis: 2016
Clinical Features - Cutaneous

- Heliotope sign
- Photodistributed poikiloderma-violaceous
- Poikiloderma over extensor surfaces-violaceous
- Gottron’s sign
- Cuticular dystrophy
- Nail fold telangiectasia
- Calcinosis cutis (complication: especially childhood)
Dermatomyositis: 2016
Clinical Features - Cutaneous
Dermatomyositis: 2016
Clinical Features - Cutaneous

Heliotope sign
Photodistributed poikiloderma-violaceous
**Poikiloderma over extensor surfaces-violaceous**
Gottron’s sign
Cuticular dystrophy
Nail fold telangiectasia
Calcinosis cutis (complication: especially childhood)
Dermatomyositis: 2016
Clinical Features - Cutaneous
Dermatomyositis: 2016
Clinical Features - Cutaneous

Heliotope sign
Photodistributed poikiloderma-violaceous
Poikiloderma over extensor surfaces-violaceous
Gottron’s sign
Cuticular dystrophy
Nail fold telangiectasia
Calcinosis cutis
  (complication: especially childhood)
Dermatomyositis: 2016
Clinical Features - Cutaneous
Dermatomyositis: 2016
Clinical Features - Cutaneous

Heliotope sign
Photodistributed poikiloderma-violaceous
Poikiloderma over extensor surfaces-violaceous
Gottron’s sign
Cuticular dystrophy
**Nail fold telangiectasia**
Calcinosi cutis (complication: especially childhood)
Dermatomyositis: 2016
Clinical Features - Cutaneous
Heliotope sign
Photodistributed poikiloderma-violaceous
Poikiloderma over extensor surfaces-violaceous
Gottron’s sign
Cuticular dystrophy
Nail fold telangiectasia

Calcinosis cutis (complication: especially childhood)
Dermatomyositis: 2016
Clinical Features - Cutaneous
Dermatomyositis: 2016
Selected Systemic Aspects

- Articular disease - if erosive, implies overlap
- Dysphagia - proximal is related to myositis true distal esophageal disease suggests overlap
- Lung disease - 15-30% diffuse interstitial fibrosis (Jo-1 antibody)
**REVISED CLASSIFICATION SYSTEM FOR THE IDIOPATHIC INFLAMMATORY DERMATOMYOPATHIES**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatomyositis</td>
<td>Adult-onset</td>
</tr>
<tr>
<td></td>
<td>Classic DM</td>
</tr>
<tr>
<td></td>
<td>Classic DM with malignancy</td>
</tr>
<tr>
<td></td>
<td>Classic DM as part of an overlapping connective tissue disorder</td>
</tr>
<tr>
<td></td>
<td>Clinically amyopathic DM*</td>
</tr>
<tr>
<td></td>
<td>Amyopathic DM</td>
</tr>
<tr>
<td></td>
<td>Hypomyopathic DM</td>
</tr>
<tr>
<td>Juvenile-onset</td>
<td>Classic DM</td>
</tr>
<tr>
<td></td>
<td>Clinically amyopathic DM</td>
</tr>
<tr>
<td></td>
<td>Amyopathic DM</td>
</tr>
<tr>
<td></td>
<td>Hypomyopathic DM</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Isolated polymyositis</td>
</tr>
<tr>
<td></td>
<td>Polymyositis as part of an overlapping connective tissue disorder</td>
</tr>
<tr>
<td></td>
<td>Polymyositis associated with internal malignancy (?)†</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td></td>
</tr>
</tbody>
</table>

*Both adult-onset and juvenile-onset amyopathic DM and hypomyopathic DM can be further subcategorized as “provisional” and “confirmed” when patients have biopsy-confirmed hallmark cutaneous manifestations of DM without muscle weakness and with normal muscle enzymes for ≥6 months (provisional) or 24 months (confirmed).†Although more recent population-based studies have clearly confirmed that adult-onset classic DM is associated with a significant risk for internal malignancy, these same studies have questioned whether such a relationship exists for polymyositis.

Table 42.1 Revised classification system for the idiopathic inflammatory dermatomyopathies. This classification scheme recognizes, with equal weighting, the cutaneous and muscle manifestations of this group of disorders.
Dermatomyositis 2016
Pathogenesis

**GENETICS**

- Monozygotic twins affected
- Associated human leukocyte antigens (HLA)
  - HLA-DR3 and B8 (juvenile dermatomyositis)
  - HLA-DR52 (patients with anti-Jo1 antibodies)
  - HLA DR7 and -DRw53 (patients with anti-Mi-2 antibodies)
  - HLA B14 and -B40 (adults with dermatomyositis overlap)
  - HLA – DRB1*15021 (Japanese with juvenile dermatomyositis)
- TNF-α 308A allele polymorphism
Histopathologic findings in skin and muscle (CD8⁺ lymphocytes)

Lymphocyte-mediated experimental myositis in mice

Increased Ki-67 and p53 expression in keratinocytes after UVB irradiation

Increased CD40 expression on muscle cells

Decreased circulating CD54 (ICAM-1)-positive lymphocytes

Fas ligand on T cells and Fas receptor on muscle cells

MHC Class I overexpressed in affected muscle tissues

Elevated expression of COX-1, COX-2, and 5-LOX mRNA in affected muscle tissues
HUMORAL IMMUNITY

- Association with autoimmune diseases (Hashimoto’s thyroiditis, Graves’ disease, myasthenia gravis, type I diabetes mellitus, primary biliary cirrhosis, dermatitis herpetiformis, vitiligo, and other autoimmune connective tissue diseases)

- Myositis-specific antibodies versus antibodies against aminoacyl-tRNA synthetases, non-synthetases, cytoplasmic antigens, and nuclear antigens. Examples include: antisynthetase, anti-Jo-1 (lung disease), and anti-Mi-2 (most specific for dermatomyositis)
INFECTIOUS PRECIPITANTS\textsuperscript{24,25}

- Seasonal variation
- Picornavirus substrate for aminoacyl-tRNA synthetases
- \textit{Escherichia coli}, muscle protein and capsid protein of a picornavirus that induces mouse myositis all have some homology of amino acid sequences with Jo-1
- Echovirus infection in patients with hypogammaglobulinemia
- Coxsackievirus-9 myositis
Dermatomyositis 2016
Pathogenesis (Cont.)

DRUG AND VACCINE PRECIPITANTS\textsuperscript{26-31}

- Hydroxyurea, D-penicillamine, TNF-\(\alpha\) inhibitors, nonsteroidal anti-inflammatory drugs, lipid-lowering drugs (statins >gemfibrozil), cyclophosphamide, BCG vaccine; single case reports of phenytoin, alfuzosin (\(\alpha\)-agonist for BPH), omeprazole, ipecac (repeated exposures), interferon-\(\alpha\)-2b, tegafur, etoposide, articaine, sulfacetamide sodium ophthalmic drops

MALIGNANCY ASSOCIATION (ADULTS)\textsuperscript{32,33}
Dermatomyositis: 2016
Laboratory Aspects

- Sedimentation rate only elevated in 50%
- Elevated: CPK, Aldolase, urine creatine, serum myoglobin, rarely urine myoglobin, other serum enzymes
- Positive ANA (90+%), anti-Jo-1 (25%), anti-Mi-1 and anti-Mi-2
- Negative anti-DNA
<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Target antigen function</th>
<th>Clinical phenotype</th>
<th>Autoantibody frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Aminoacyl-tRNA</td>
<td>Intracytoplasmic protein synthesis</td>
<td>Antisynthetase syndrome (myositis, mechanic’s hands, Gottron’s papules, arthritis, fever, Raynaud’s phenomenon, high frequency of interstitial lung disease)</td>
<td>up to 20%</td>
</tr>
<tr>
<td>Synthetases (e.g. anti-Jo-1 [histidyl], anti-PL-7 [theonyl]; see Ch. 40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>Protein translocation</td>
<td>Acute-onset necrotizing myopathy (severe weakness, high CK), may be refractory to treatment</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>Helicase – transcription</td>
<td>Adult DM and juvenile DM (hallmark is cutaneous disease, milder muscle disease with good response to treatment)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10</td>
</tr>
<tr>
<td>Anti-p155/140</td>
<td>See Ch. 40</td>
<td>Cancer-associated myositis in adult DM, severe cutaneous disease in adult DM and juvenile DM</td>
<td>80 (amyos); 20–30 (classic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>~25</td>
</tr>
<tr>
<td>Anti-p140</td>
<td>Likely NXP-2 – nuclear transcription, RNA metabolism</td>
<td>Juvenile DM with calcinosis</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>~25</td>
</tr>
<tr>
<td>Anti-SCAE</td>
<td>Post-translational modification</td>
<td>Adult DM, may present with clinically amyopathic DM</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Anti-CADM-140 (MDA5)</td>
<td>Innate immunity</td>
<td>Clinically amyopathic DM; rapidly progressive interstitial lung disease</td>
<td>10–15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 42.4 Serum autoantibodies in adult and juvenile dermatomyositis (DM). The autoantigen CADM-140 was subsequently found to be identical to two previously identified gene products, interferon induced with helicase C domain protein 1 (IFIH1) and melanoma differentiation-associated gene 5 (MDA5). CADM, cancer-associated dermatomyositis; CK, creatine kinase; NA, not applicable; NXP-2, nuclear matrix protein NXP2; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle. Adapted from ref. 35.
Dermatomyositis: 2016
Muscle Biopsy

- Can provide evidence supporting diagnosis
- Can definitively exclude certain other conditions in the differential
- Incisional vs needle biopsy
- Quadriceps, triceps
Dermatomyositis: 2016
Histopathologic Aspects

- **Skin**: Epidermal atrophy, interface change, vascular dilatation, occasional mucin deposition
- **Muscle**: Mixed/primarily lymphocytic infiltrate, necrosis of muscle fibers, fibrosis, phagocytosis, regeneration
Dermatomyositis: 2016
Histopathologic Aspects
Abnormal in about 90% of active cases

Characteristic triad

May support diagnosis and help exclude other conditions
Dermatomyositis: 2016

Prognosis

- Precorticosteroid era: 50-60% mortality
- Newcastle series: Childhood mortality 5%, Overall mortality 28% (6 years)
- Johns Hopkins survey: Similar to Newcastle overall mortality 27% (8 years)
- Variable morbidity data in childhood PM/DM from 1/3 with severe impairment versus mean of no objective impairment
- Our data on 20 children after 2-20 years
Dermatomyositis: 2016

Classic clinicopathologic disease in patients with normal muscle enzymes

- **Group 1**: Cutaneous changes only: 5 patients (1-10 years)
- **Group 2**: Cutaneous changes only at baseline with subsequent evolution of myositis: 2 patients (1/2-2 1/2 years)
- **Group 3**: Cutaneous changes with normal muscle enzymes but invasive tests revealed myositis: 4 patients (4 positive EMG, 2 positive biopsy)

Dermatomyositis: 2016

Magnetic Resonance Imaging
Dermatomyositis: 2016

Ultrasound
Dermatomyositis Update: 2016

Therapeutic Ladder

- Systemic Corticosteroids (2)
  - Prednisone 1mg/kg/day taper to 1/2 over 6 months
  - Then attempt to reach qod dosing
  - Usually required for 2 years
  - Pulse and split dose options
- Methotrexate low dose weekly pulse (2)
- Azathioprine 2-3 mg/kg/day(3)
- IVIG(1)

Key
(1) - Double blind studies
(2) - Clinical series
(3) - Anecdotes
# Therapeutic Ladder for Dermatomyositis

## SYSTEMIC THERAPY

### Oral prednisone:
1 mg/kg/day tapered to 50% over 6 months and to zero over 2-3 years (1)
Option to use pulse, split-dose, or alternate-day (2)

### Methotrexate:
5-20 mg weekly (2)

### Azathioprine:
2-3 mg/kg/day (1)

### Others:
- High-dose IvIg (2 g/kg/month) (1)
- Pulse cyclophosphamide (0.5-1.0 g/m² monthly) (2)
- Chlorambucil (4 mg/day) (2)
- Cyclospporine (3-5 mg/kg/day) (2)
- Tacrolimus (0.12 mg/kg/day) (3)
- Mycophenolate mofetil (1 g twice daily) (2)
- Sirolimus (5 mg/day x 2 weeks, 2 mg/day x 2 weeks, then 1 mg/day) (3)
- Infliximab (5-10 mg/kg every 2 weeks initially) (3)
- Etanercept (3)†
- Rituximab (375 mg/m²/infusion for 4 weekly infusions) (2)
- Fludarabine (3)
- Hematopoietic stem cell transplantation (3)
- Plasmapheresis (3)†

†Double-blind trial showed no benefit.
**Therapeutic Ladder for Dermatomyositis**

**CUTANEOUS LESIONS**

- Sunscreens (high sun protection factor including protection against UVA) (3)
- Topical corticosteroids (3)
- Topical tacrolimus (3)
- Hydroxychloroquine (200 mg twice daily; increased frequency of drug eruptions in patients with dermatomyositis) (2)
- Hydroxychloroquine (200 mg twice daily) plus quinacrine (100 mg/day) (3)
- Low-dose weekly methotrexate (5-15 mg weekly) (2)
- Mycophenolate mofetil (3)
- High-dose IVIg (2 g/kg/month) (1)
- Retinoids (3)
- Dapsone (3)
- Thalidomide (3)
- Leflunomide (3)
- Antiestrogens (e.g. Tamoxifen, anastrazole) (3)
- TNF-α inhibitors (e.g. Infliximab, etanercept) (3)*
- Rituximab (3)
- Tacrolimus (3)

*Reported cause of drug-induced dermatomyositis.
Scleroderma Update: 2016

- Greek: “Hard skin”
- Rare autoimmune disease
- Idiopathic
- High morbidity
- Variable mortality
- Spectrum of disease: Morphea, limited disease (CREST), diffuse disease (PSS)
Scleroderma Update: 2016

ACR Diagnostic Criteria

- **Major criterion**
  - **Proximal scleroderma**
    Indurated, hard skin. Often the skin is shiny with loss of cutaneous surface markings. Loss of elasticity occurs. Hyper- and hypopigmentation are common.

- **Minor criteria**
  - **Sclerodactyly**
  - **Digital pitted scars or loss of substance of the finger pad**
  - **Bibasilar pulmonary fibrosis**

Diagnosis is 97% certain with one major, or two minor or more criteria present. There are no specific diagnostic criteria for localized cutaneous scleroderma, scleroderma variants, overlap syndromes, and environmentally induced scleroderma at this time.
Local Forms
- Linear scleroderma
- Generalized morphea
- Morphea (plaque, guttate, or subcutaneous)

Systemic Sclerosis
- Limited (no truncal involvement)
- Diffuse (widespread skin involvement)
Differential Diagnosis of Sclerodermoid Conditions

Clinical Features

**MUCINOSES**

- **Scleredema**
  Induration of the upper back, neck and face; occasional internal involvement (see Ch. 46)

- **Scleromyxedema**
  Waxy papules (often in a linear array): diffuse induration favoring the face, upper trunk, arms and thighs; monoclonal gammopathy; neurologic, gastrointestinal and pulmonary involvement (see Ch. 46)
Differential Diagnosis of Sclerodermoid Conditions

Clinical Features

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic GVHD*</td>
<td>Morpheaform plaques favoring the trunk, which may become generalized; eosinophilic fasciitis (see Ch. 52)</td>
</tr>
<tr>
<td>Eosinnophilic faciitis</td>
<td>Symmetric induration with a “pseudo-cellulite” appearance on the extremities (sparing hands and feet) (see text)</td>
</tr>
<tr>
<td>Generalized morphea*</td>
<td>Expansion and coalescence of morphea plaques to involve a large portion of the trunk and extremities (see Ch. 44)</td>
</tr>
<tr>
<td>Fibroblastic rheumatism</td>
<td>Sclerodactyly; fibrotic nodules on the hands</td>
</tr>
</tbody>
</table>
Differential Diagnosis of Sclerodermoid Conditions

Clinical Features

**PARANEOPLASTIC**

- POEMS syndrome
  - Sclerotic skin on the extremities (see Ch. 114)
- Amyloidosis (primary systemic)^†
  - Diffuse induration favoring the face, distal extremities and trunk (see Ch. 47)
- Carcinoid syndrome
  - Sclerotic skin on the legs (see Table 53.3)

**NEOPLASTIC**

- Carcinoma *en cuirasse*
  - Sclerodermoid encasement of the chest by metastatic carcinoma (usually breast cancer)

**METABOLIC**

- Diabetic cheiroarthropathy
  - Thickened skin and limited mobility of the hands (see Table 53.4)
- Porphyria cutanea tarda^*
  - Morpheaform plaques in sun-exposed areas (see Chs 44 & 49)
<table>
<thead>
<tr>
<th>Neurologic</th>
<th>Toxin-Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflex sympathetic dystrophy*</td>
<td>Associated with exposure to gadolinium-based contrast agents (US, 1997-present; now worldwide) (see text)</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>Associated with L-tryptophan ingestion (US, 1989) (see text)</td>
</tr>
<tr>
<td>Nephrogenic systemic fibrosis*</td>
<td>Associated with toxic oil ingestion (Spain, 1981) (see text)</td>
</tr>
<tr>
<td>Eosinophilia-myalgia syndrome</td>
<td></td>
</tr>
<tr>
<td>Toxic oil syndrome*</td>
<td></td>
</tr>
</tbody>
</table>
Differential Diagnosis of Sclerodermoid Conditions
Clinical Features

**DRUG-OR-CHEMICAL-INDUCED (SEE TEXT)**

- **Bleomycin***
  - Acrosclerosis, Raynaud’s phenomenon; pulmonary fibrosis (more common, usually no concurrent skin lesions)

- **Taxanes**
  - Edema followed by sclerosis of the lower extremities; acrosclerosis

- **Vinyl chloride chlorinated hydrocarbons***
  - Acrosclerosis, acral fibrotic papulonodules, Raynaud’s phenomenon, acro-osteolysis; pulmonary fibrosis

**VENOUS INSUFFICIENCY**

- **Lipodermatosclerosis***
  - Woody induration and hemosiderin pigmentation on the lower legs; may also involve the pannus (see Ch. 100)
Differential Diagnosis of Sclerodermodermoid Conditions

Clinical Features

**GENETIC DISORDERS**

- **Restrictive dermopathy§**
  - Tight, thin skin over the entire body; joint contractures; *LMNA* or *ZMPSTE24* mutations

- **Hutchinson-Gilford progeria**
  - Sclerotic skin on the lower trunk, buttocks and thighs; *LMNA* mutations (see Ch. 63)

- **Werner syndrome**
  - Tight, sclerotic skin on the distal extremities; *RECQL2* mutations (see Ch. 63)

- **Stiff skin syndrome**
  - Fibrosis of the skin/fascia of the buttocks and thighs with hip contractures (see text)

- **Phenylketonuria**
  - Sclerotic skin on the thighs and buttocks with hip contractures (see Ch. 63)

- **Winchester syndrome***
  - Diffuse, symmetric, leathery skin thickening; fibrotic plaques or bands; *MMP2* mutations (see Table 70.2)

- **Ataxia-telangiectasia**
  - Tight, sclerotic facial skin (see Ch. 60)
Differential Diagnosis of Sclerodermoid Conditions

Clinical Features

**GENETIC DISORDERS (CONT.)**

- **Huriez syndrome**
  - Sclerodactyly; atrophic skin on dorsal surfaces on hands and feet; palmoplantar keratoderma (see Ch. 58)

- **H syndrome**
  - Hypertrichosis in association with areas of hyperpigmentation and induration (primarily lower trunk and lower extremities), sensorineural hearing loss, short height, heart anomalies, hepatosplenomegaly, scrotal masses, hypergonadotriptic hypogonadism, antibody-negative insulin-dependent diabetes mellitus, facial telangiectasias; mutations in \textit{SLC29A3} which encodes nucleoside transporter hENT3

Can overlap with morpheaform disorders, which are listed in Table 44.1

†Primary cutaneous amyloidosis can also occur in patients with systemic sclerosis and Generalized morphea.

§Sclerodermoid changes are typically present at birth.
Differential Diagnosis: Sclerodermoid Conditions

- Genetic (PKU, Progeria, Werner’s, Rothmund-Thompson)
- Environmental (Vibration, Polyvinyl chloride, Silica, aeromatic hydrocarbons, Spanish oil, L-tryptophan, Silicone)
- Metabolic (PCT, Amyloidosis, Diabetes)
- Immunologic (GVH, Scleromyxedema)
- Drugs (Bleomycin, INH, others)
- Malignancy (Carcinoid, melanoma, other, paraneoplastic)
- Post infections (Scleredema, Acrodermatitis chronica atrophicans, Partial lipodystrophy)
- Neurological (Limb immobilization, Spinal injury)
- Radiation (Breast CA, Chernobyl nuclear accident)
- Renal disease (nephrogenic systemic fibrosis)
Scleroderma: Update 2016
Morphea Overview

- Cutaneous form of scleroderma
- No recognized internal organ involvement
- Rarely coexists with connective tissue vascular diseases
- Thought not to progress to PSS
- Debate exists in children
Not fatal, but produces considerable morbidity including contractures and skin textural change and disfigurement

ANA and/or ssDNA maybe positive, blood eosinophiliaia and elevated IgG may relate to prognosis
No treatment has become widely accepted as effective

Physical therapy is crucial to prevent contractures

In the absence of good double blind prospective placebo controlled trials much of the remaining points in the discussion will be anecdotal
Morphea - Clinical Forms
Plaque Type Morphea
Diffuse Type Morphea
Linear and En Coupe de Sabre
Type Morphea
Scleroderma Update: 2016
Histopathologic Features
Localized Scleroderma: 2016
Topical Treatment - General

- Emollients (3)
- Topical corticosteroids (3)
- Superpotent topical corticosteroids (2)
- Topical calcipotriene plus occlusion (2)
- Topical imiquimod (3)
- Topical tacrolimus plus keratocytic (3)
- Intrallesional corticosteroids (3)
- Physical therapy (3)
- PUVA and other phototherapy including UVA-1 (2)
- Methotrexate (2)
- Prednisone taper/methotrexate (2)
- Other
Scleroderma Update: 2016
Systemic Scleroderma Clinical Features
Scleroderma Update: 2016
Systemic Scleroderma Clinical Features
Scleroderma Update: 2016

Systemic Features

- Raynaud’s phenomenon
- Pulmonary hypertension, fibrosis
- GI: Esophagus, small intestine (malabsorption, bacterial overgrowth)
- Cardiac: Pericarditis, myocarditis, conduction abnormalities
- Renal: Severe arterial hypertension
- Arthralgias and myalgias
Pathogenesis

- Unknown
- Viral etiology theories
- Borrelia theories for morphea
- Environmental theories
- Immunologic/vascular theories
- Microchimerism (Fetal CD3+ cells in maternal circulation with GVH-like response)
Scleroderma Update: 2016
Pathogenesis (Cont.)

- Genetic factors - unclear
- Microvascular targets - capillary damage, adhesion molecules, perivascular infiltrates
- Immune dysfunction - T cell subsets, cytokines, autoantigens to topoisomerase I, centromeric proteins and RNA polymerases
- Connective tissue fibrosis - TGF-beta, CTGF and collagen receptors (alpha 1 beta 1, alpha 2 beta 2)
Fig. 43.1 Interactions between endothelial cells, leukocytes and fibroblasts in scleroderma pathogenesis. CTGF, connective tissue growth factor; EC, endothelial cell; ECM, extracellular matrix; IFN, interferon; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor. Genetic susceptibility loci that may increase the risk of developing scleroderma include a region on chromosome 15q (which contains the fibrillin-1 gene) as well as polymorphisms in STAT4 and the promotor for CTGF.

## Table 43.1 Major clinical and laboratory manifestations of systemic sclerosis and other selected conditions characterized by cutaneous induration

<table>
<thead>
<tr>
<th></th>
<th>Systemic sclerosis</th>
<th>Morphea</th>
<th>Eosinophilic fasciitis</th>
<th>Sclerema</th>
<th>Scleromyxedema</th>
<th>NSF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major clinical variants</strong></td>
<td>Limited</td>
<td>Plaque-type</td>
<td>Post-infectious (type I)</td>
<td>Monoclonal gammapathy-associated (type II)</td>
<td>Diabetes mellitus-associated (type III)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diffuse</td>
<td>morphea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linear morphea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Generalized morphea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Raynaud’s phenomenon</strong></td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Symmetric induration</strong></td>
<td>++*</td>
<td></td>
<td>++*</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Sclerodactyly</strong></td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Facial involvement</strong></td>
<td>+</td>
<td>plaque-type and generalized</td>
<td>± types I and II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>linear (en coup de sabre)</td>
<td>type III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic involvement</strong></td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>Antinuclear antibodies</strong></td>
<td>++</td>
<td>± generalized and linear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>plaque-type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anticentromere antibodies</strong></td>
<td>+ limited</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-topoisomerase I (Scl-70) antibodies</strong></td>
<td>+ diffuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monoclonal gammapathy</strong></td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td>+ type II</td>
<td></td>
</tr>
<tr>
<td><strong>Spontaneous remission</strong></td>
<td>–</td>
<td>++ plaque-type</td>
<td>++ type I</td>
<td></td>
<td>± types II and III</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ generalized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>± linear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*May be preceded by edematous phase.

1 With improved renal function.

NSF, nephrogenic systemic fibrosis; ++, almost always; +, common; ±, sometimes; −, rare or unusual.

Courtesy, Vincent Falanga, MD.
Therapy - General

- Therapy for specific features (Raynaud’s, esophageal reflex, hypertension)
- Therapies used for Raynaud’s phenomenon
  - Avoid cold, stop smoking, biofeedback
  - Calcium channel blockers - (e.g. Nifedipine extended release etc.)
  - Nitroglycerin ointment 2% - (1/4-1 inch q6h)
  - Hydralazine 40-50mg/day
  - ACE inhibitors (e.g. Captopril 25-150mg tid; Prevent renal crisis)
  - Botulinum toxin type A
  - Angiotensin-receptor blocker (losartan 50mg/day)
  - Prostaglandins (egilopros, epoprostenolol)
  - Iloprost (prostacyclin analog IV pulse)
  - Pentoxifylline 400mg tid
  - Sildenafil (phosphodiesterase inhibitor)
  - Endothelin inhibitor (Bosentan)
  - Tyrosine kinase inhibitor (imatinib)
<table>
<thead>
<tr>
<th>Symptoms/signs*</th>
<th>Studies</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Interstitial lung disease</td>
<td>Interstitial lung disease: Pulmonary function tests, including DLCO&lt;sup&gt;1&lt;/sup&gt; High-resolution CT&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Interstitial lung disease: immunosuppression, primarily cyclophosphamide or mycophenolate mofetil</td>
</tr>
<tr>
<td>• Pulmonary artery hypertension</td>
<td>Pulmonary artery hypertension: Echocardiogram Right heart catheterization</td>
<td>Pulmonary artery hypertension: vasodilators including endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan), prostacyclin analogues (iloprost inhaled), epoprostenol (IV), treprostinil (sc), and PDE5 inhibitors (sildenafil, tadalafil)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath, dyspnea on exertion, palpitations Signs of right- or left-sided CHF (e.g., tachypnea, rales, peripheral edema; see above)</td>
<td>Electrocardiogram Right heart catheterization</td>
<td>Diuretics, ACE inhibitors, β-blockers (unless contraindicated), angiotensin II receptor blockers, aldosterone antagonists</td>
</tr>
<tr>
<td>Renal, including scleroderma renal crisis&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Headache, blurry vision Hypertension</td>
<td>Blood pressure BUN, creatinine, urinalysis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Dyspepsia, dysphagia, postprandial bloating, constipation, diarrhea Signs of malnutrition</td>
<td>Upper gastrointestinal series (barium swallow) with small bowel follow-through Manometry Endoscopy Malabsorption evaluation</td>
</tr>
</tbody>
</table>

*Patients may be asymptomatic.
<sup>1</sup>At baseline and every 6–12 months for first five years after initial diagnosis, then yearly.
<sup>2</sup>May need to consider withdrawal of calcium channel blockers.

Table 43.5 Evaluation and treatment of internal organ involvement in patients with systemic sclerosis. ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen; CHF, congestive heart failure; CT, computerized tomography; DLCO, diffusion capacity of carbon monoxide; IV, intravenous; PDE5, phosphodiesterase type 5; sc, subcutaneous.
Scleroderma: Update 2016
Therapy Possible Systemic Agents

- Minocycline
- Hydroxychloroquine
- Quinacrine
- Colchicine
- Phenytoin
- D-Penicillamine
- Aminobenzoate potassium (Potaba)
- PUVA and other phototherapy
- Gamma or alpha interferon
- Relaxin
- Bosentan (oral endothelin receptor antagonist)
Scleroderma: Update 2016 Therapy
Possible Systemic Agents (Continued)

- Prednisone
- Methotrexate
- Azathioprine
- Mycophenolate mofetil
- Cyclophosphamide
- Chlorambucil
- Cyclosporine
- Imatinib (Gleevec – Dual transforming growth factor beta and platelet derived growth factor inhibitor)
- Extracorporeal photophoresis
- Stem cell transplantation
Scleroderma Update: 2016
Possible Systemic Agents (Cont.)

- Thalidomide derivatives
- TNF alpha inhibitors
- Rituximab
- IVIG
- Other
- Biological therapies directed at these targets:
  - TGF-beta
  - Connective tissue growth factor
  - IL-4, IL-13, MCP-1
  - Endothelin
Lichen Sclerosus

Key Features

- Sclerotic white plaques with epidermal atrophy and, in extramucosal sites, follicular plugging
- Most commonly affects female or male genitalia, less often non-genital skin
- May cause scarring of the vaginal introitus or phimosis
- Severe pruritus may occur
- No systemic manifestations
<table>
<thead>
<tr>
<th>Treatment modalities</th>
<th>Morphoea Efficacy</th>
<th>Level of evidence</th>
<th>Lichen sclerosis Efficacy</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>+</td>
<td>3</td>
<td>+++ (ultrapotent)</td>
<td>1</td>
</tr>
<tr>
<td>Intraleisonal corticosteroids</td>
<td>+</td>
<td>3</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>Topical calcineurin inhibitors</td>
<td>+ (early lesions)</td>
<td>2</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin A analogues</td>
<td>+</td>
<td>3</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin D analogues</td>
<td>+</td>
<td>3</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>Testosterone</td>
<td>No experience</td>
<td>0</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>Progesterone</td>
<td>No experience</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Intraleisonal interferon-γ</td>
<td>0</td>
<td>1</td>
<td>No experience</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>++ (approx. 5% of patients)</td>
<td>3</td>
<td>No experience</td>
<td>3</td>
</tr>
<tr>
<td>Hydroxy-/chloroquine</td>
<td>No experience</td>
<td>0</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>+</td>
<td>3</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>Vitamin A analogues*</td>
<td>+</td>
<td>3</td>
<td>++</td>
<td>1</td>
</tr>
<tr>
<td>Vitamin D analogues</td>
<td>0</td>
<td>1</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0</td>
<td>3</td>
<td>No experience</td>
<td></td>
</tr>
<tr>
<td>Penicillamine</td>
<td>++</td>
<td>3</td>
<td>No experience</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>++</td>
<td>2</td>
<td>No experience</td>
<td></td>
</tr>
<tr>
<td><strong>Phototherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral photochemotherapy</td>
<td>++</td>
<td>3</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>Bath photochemotherapy</td>
<td>++</td>
<td>3</td>
<td>+</td>
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<td>Cream photochemotherapy</td>
<td>++</td>
<td>3</td>
<td>+</td>
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<tr>
<td>UVA1</td>
<td>+++</td>
<td>2</td>
<td>++</td>
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</tr>
<tr>
<td>Photodynamic therapy</td>
<td>+</td>
<td>3</td>
<td>++</td>
<td>2</td>
</tr>
<tr>
<td>Extracorporeal photopheresis</td>
<td>+</td>
<td>3</td>
<td>No experience</td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO₂ laser</td>
<td>No experience</td>
<td>++</td>
<td>Selected patients</td>
<td>3</td>
</tr>
<tr>
<td>Surgery</td>
<td>Selected patients</td>
<td></td>
<td>Selected patients</td>
<td></td>
</tr>
<tr>
<td>Physical therapy</td>
<td>Important</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*E.g. acetretin.

Table 44.2 Treatment of morphea and lichen sclerosus. ++++, Highly effective; ++, effective; +, moderately effective; 0, low efficacy or ineffective. 1, prospective controlled trial; 2, retrospective study or large case series; 3, small case series or individual case reports.
Sarcoidosis

Key Features

- A systemic granulomatous disorder of unknown origin that most commonly involves the lungs
- Cutaneous manifestations of sarcoidosis are seen in up to one-third of patients, and they may be the first clinical sign of the disease
- Red-brown to violaceous papules and plaques appear most often on the face, lips, neck, upper back and extremities
- Variants of sarcoidosis include subcutaneous, lupus pernio and ulcerative
- Erythema nodosum is a non-specific inflammatory skin finding associated with acute, transient sarcoidosis
- Histologically, sarcoidosis is characterized by non-caseating epitheloid granulomas, usually without surrounding lymphocytic inflammation (i.e. ‘naked’ granulomas)
Sarcoidosis: Systemic Features

- SURT
- Intrathoracic
- Ocular
- Lymph Nodes

- Musculoskeletal
- Neurosarcoidosis
- Hepaticsarcoidosis
- Cardiac
- Endocrine metabolic
<table>
<thead>
<tr>
<th></th>
<th>Sarcoidosis</th>
<th>Granuloma annulare</th>
<th>Necrobiosis lipoidica</th>
<th>AEGCG</th>
<th>Cutaneous Crohn's disease</th>
<th>Rheumatoid nodule*</th>
<th>Interstitial granulomatous dermatitis*</th>
<th>Palisading neutrophilic and granulomatous dermatitis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical location</td>
<td>Superficial and deep dermis*</td>
<td>Superficial and mid dermis*</td>
<td>Entire dermis, subcutis</td>
<td>Superficial and mid dermis</td>
<td>Superficial and deep dermis</td>
<td>Deep dermis, subcutis</td>
<td>Mid and deep dermis</td>
<td>Entire dermis</td>
</tr>
<tr>
<td>Granuloma pattern</td>
<td>Tubercle with few peripheral lymphocytes (&quot;naked&quot;)</td>
<td>Palisading or interstitial</td>
<td>Diffuse palisading and interstitial; horizontal &quot;tiers&quot;</td>
<td>Palisading, irregular</td>
<td>Tubercle with surrounding lymphocytes</td>
<td>Palisading</td>
<td>Palisading in small &quot;rosettes&quot;</td>
<td>Palisading; prominent neutrophils and leukocytoclasia</td>
</tr>
<tr>
<td>Necrobiosis (altered collagen)</td>
<td>No</td>
<td>Yes (&quot;blue&quot;)</td>
<td>Yes (&quot;red&quot;)</td>
<td>No</td>
<td>No</td>
<td>Yes (&quot;red&quot;)</td>
<td>Yes (&quot;blue&quot;)</td>
<td>Yes (&quot;blue&quot;)</td>
</tr>
<tr>
<td>Giant cells</td>
<td>Yes</td>
<td>Variable</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Elastolysis</td>
<td>No</td>
<td>Variable</td>
<td>Variable</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Elastophagocytosis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Asteroid bodies</td>
<td>Yes</td>
<td>Variable</td>
<td>Variable</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Mucin</td>
<td>No</td>
<td>Yes</td>
<td>Minimal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Minimal</td>
<td>Variable</td>
</tr>
<tr>
<td>Extracellular lipid</td>
<td>No</td>
<td>Variable</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Variable</td>
<td>No</td>
</tr>
<tr>
<td>Vascular changes</td>
<td>No</td>
<td>Variable</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*See Chapter 45.
<sup>1</sup>Subcutaneous variant can also occur.

Table 93.2 Histologic features of the major granulomatous dermatitides. Interstitial granulomatous dermatitis and palisading neutrophilic and granulomatous dermatitis are often considered two ends of a spectrum. Tan-shaded area is not covered in this chapter. AEGCG, annular elastolytic giant cell granuloma.

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### TREATMENT OF CUTANEOUS SARCOIDOSIS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical, intralesional or systemic corticosteroids (2)</td>
<td>(2)</td>
</tr>
<tr>
<td>Topical calcineurin inhibitors (3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Minocycline (2)</td>
<td>(2)</td>
</tr>
<tr>
<td>Systemic hydroxychloroquine or chloroquine (2)</td>
<td>(2)</td>
</tr>
<tr>
<td>IntraleSIONAL chloroquine (3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Allopurinol (3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Isotretinoin (3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Methotrexate (2)</td>
<td>(2)</td>
</tr>
<tr>
<td>PUVA (psoralen plus UVA) (3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Thalidomide (2)</td>
<td>(2)</td>
</tr>
<tr>
<td>TNF-α inhibitors (adalimumab, infliximab, etanercept)* (3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Leflunomide (2)</td>
<td>(2)</td>
</tr>
<tr>
<td>Mycophenolate mofetil (3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Surgical excision (3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Pulsed dye or CO₂ laser (3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Photodynamic therapy (3)</td>
<td>(3)</td>
</tr>
</tbody>
</table>

*Can trigger sarcoidosis.

---

**Table 93.3 Treatment of cutaneous sarcoidosis.** Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. TNF, tumor necrosis factor.
Granuloma Annulare

Key Features

- Small grouped papules assuming an annular configuration often in a symmetrical and acral distribution
- Seen primarily in children and young adults
- Clinical variants include localized, generalized, micropapular, nodular, perforating, patch and subcutaneous forms
- Reports of an association with diabetes mellitus are controversial
- Histopathologic specimens show infiltrative or palisading granulomatous dermatitis with focal degeneration of collagen and elastin and deposition of mucin
### Treatment of Granuloma Annulare

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical corticosteroids</td>
<td>(3)</td>
</tr>
<tr>
<td>Intraleisional corticosteroids</td>
<td>(2)</td>
</tr>
<tr>
<td>Topical calcineurin inhibitors</td>
<td>(3)</td>
</tr>
<tr>
<td>Topical imiquimod</td>
<td>(3)</td>
</tr>
<tr>
<td>Cryosurgery</td>
<td>(2)</td>
</tr>
<tr>
<td>Hydroxychloroquine or chloroquine</td>
<td>(2)</td>
</tr>
<tr>
<td>Niacinamide (nicotinamide)</td>
<td>(3)</td>
</tr>
<tr>
<td>Minocycline + ofloxacin + rifampin*</td>
<td>(3)</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>(3)</td>
</tr>
<tr>
<td>Intraleisional interferon</td>
<td>(3)</td>
</tr>
<tr>
<td>5-lipoxygenase inhibitor (zileuton) + vitamin E†</td>
<td>(3)</td>
</tr>
<tr>
<td>Dapsone</td>
<td>(3)</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>(3)</td>
</tr>
<tr>
<td>PUVA (psoralen plus UVA) or UVA1</td>
<td>(2)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>(3)</td>
</tr>
<tr>
<td>TNF-α inhibitors (adalimumab, infliximab)</td>
<td>(3)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>(3)</td>
</tr>
<tr>
<td>Fumaric acid esters</td>
<td>(3)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>(3)</td>
</tr>
<tr>
<td>Photodynamic therapy with topical 5-aminolevulinic acid</td>
<td>(3)</td>
</tr>
<tr>
<td>CO₂ laser</td>
<td>(3)</td>
</tr>
<tr>
<td>Surgical excision</td>
<td>(3)</td>
</tr>
</tbody>
</table>

*Administered monthly: minocycline (100 mg), ofloxacin (400 mg) and rifampin (600 mg) x 3 months
†Doses of 2400 mg po daily (zileuton) and 400 IU po daily (vitamin E).

**Table 93.4 Treatment of granuloma annulare.** Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.
Treatment of Granuloma Annulare (Cont.)

- Narrowband UVB (2)
- UVA-1 (2)
- Triple antibiotic (3)
Necrobiosis lipoidica

Key Features

- Plaques with violaceous to red-brown, palpable peripheral rims and yellow-brown atrophic centers with telangiectasias
- The most common site is the shins
- Ulceration can occur following trauma
- The proportion of patients with diabetes mellitus varies from 14% to 65%
- Pathogenesis is unknown
- Pathology shows palisading granulomatous dermatitis with a ‘layered’ appearance, often with perivascular plasma cells
Necrobiosis lipoidica Treatment

- *Topical corticosteroids – pulse superpotent
- *Keratolytic topicals plus – topical tacrolimus
- *Aspirin/Dipyridomonal
- *Pentoxilfylline
- Nicrotinamide
- Clofazimune
- Misc: topical retinoids, heparin, antimalarials, thalidomide, cyclosporine, biologics, surgery, photodynamic therapy, etc