Cutaneous Vasculitis: AAD 2018

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Conflict of Interest

Amgen – Advisory Board – Honoraria
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 Types II and III</td>
<td>Petechiae</td>
<td>Palpable purpura, Livedo racemosa, Retiform purpura, Ulcers</td>
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<td>ANCA-associated</td>
<td>Microscopic polyangiitis, Wegener’s granulomatosis, Churg–Strauss syndrome, Secondary causes</td>
<td>Subcutaneous nodules, Digital necrosis</td>
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<td>Inflammatory disorders (e.g. AI-CTD)</td>
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<td>Medium-sized</td>
<td>Polyarteritis nodosa (PAN) Classic (systemic) PAN, Cutaneous PAN</td>
<td>Livedo racemosa, Retiform purpura, Ulcers, Subcutaneous nodules, Digital necrosis</td>
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<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>
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<td></td>
<td>Takayasu’s arteritis</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>
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</table>

*Cutaneous manifestations are rare.

Table 24.1 Cutaneous vasculitis classification scheme. AI-CTD, autoimmune connective tissue diseases. © 2012, Elsevier Limited. All rights reserved.
Vasculitis: 2018
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 Concensus 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 and ongoing
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 postcapillary 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 dilatation 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). Neutrophils 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 angio genesis. 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 “pauci-immune” vasculitides.
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: 2018
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: 2018
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
IgA Vasculitis (Henoch-Schönlein Purpura)

Key Features

- Most commonly occurs in children <10 years of age and in association with a preceding respiratory infection, but may also be seen in adults
- Intermittent palpable purpura on extensor extremities and buttocks
IgA Vasculitis (Henoch-Schönlein Purpura)

Key Features (Cont.)

- IgA-dominant immune deposits in walls of small blood vessels
- Arthralgias and arthritis
- Abdominal pain and/or melena
- Renal vasculitis often mild but can be chronic
- May be associated with an underlying malignancy in adults
<table>
<thead>
<tr>
<th>GENETIC POLYMORPHISMS OR MUTATIONS THAT PREDISPOSE TO HENOCH–SCHÖNLEIN PURPURA OR WEGENER’S GRANULOMATOSIS</th>
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<tr>
<td><strong>HENOCHE–SCHÖNLEIN PURPURA</strong></td>
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<tr>
<td><strong>Protein product</strong></td>
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<tr>
<td>Mannose-binding lectin (MBL)</td>
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<td>MBL-associated serine protease</td>
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<td>Interleukin-1 receptor antagonist</td>
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<td>Interleukin-1β</td>
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<td>Interleukin-8</td>
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<td>Vascular endothelial growth factor</td>
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<td>α₁-antitrypsin (deficiency)</td>
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<td><strong>Gene</strong></td>
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<td>Paired box gene 2</td>
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<td>Inducible nitric oxide synthetase 2A promoter</td>
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<td>MEFV (familial Mediterranean fever gene)</td>
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<tr>
<td><strong>Other</strong></td>
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<tr>
<td>HLA-B35 positivity – predisposes to renal disease</td>
</tr>
<tr>
<td>ICAM-1 469 K/E negative genotype – less severe gastrointestinal involvement</td>
</tr>
</tbody>
</table>

| **WEGENER’S GRANULOMATOSIS**                                  |
| PTPN22 (PR3 antibodies)                                       |
| MHC (HLA-DPB1*0401)                                           |
| CTLA4                                                        |
| Protease inhibitors                                           |
| Fc gamma                                                     |
| PR3 promoter                                                 |

Table 24.4 Genetic polymorphisms or mutations that predispose to Henoch–Schönlein purpura or Wegener’s granulomatosis. Either the gene or the protein product is listed. PR, proteinase.
Fig. 24.7 Henoch–Schönlein purpura. A Multiple pink papules on the lower extremities that are becoming purpuric. B More developed lesions with central necrosis.
Acute Hemorrhagic Edema of Infancy

Key Features

- The child is well-appearing
- Seen primarily in children between 4 and 24 months of age
- Annular, circular or targetoid purpuric plaques on the face and extremities
- Tender, non-pitting edema of acral sites
- Extracutaneous involvement rare
- Benign clinical course with spontaneous resolution within 1 to 3 weeks
# TRIGGERS AND ASSOCIATIONS IN ACUTE HEMORRHAGIC EDEMA OF INFANCY AND URTICARIAL VASCUITIS

## ACUTE HEMORRHAGIC EDEMA OF INFANCY – TRIGGERS

- Infections
  - Adenovirus
  - Coxsackievirus
  - Cytomegalovirus
  - Epstein-Barr virus
  - Herpes simplex virus
  - Hepatitis A virus
  - Measles
- Rotavirus
- Varicella zoster virus
- Campylobacter spp.
- Escherichia coli
- Mycobacterium tuberculosis
- Streptococcus spp.

## URTICARIAL VASCUITIS – ASSOCIATIONS

- Autoimmune connective tissue diseases (Sjögren's syndrome, SLE)
- Serum sickness
- Cryoglobulinemia
- Infections
  - Hepatitis B virus
  - Hepatitis C virus
  - Epstein-Barr virus
  - Lyme disease
- Medications
  - Cimetidine
  - Cocaine
  - Diltiazem
  - Etanercept
  - Fluoxetine
  - Infliximab
- Methotrexate
- NSAIDs
- Potassium iodide
- Proacainamide
- Procarbazine

- Hematologic malignancies
  - Plasma cell dyscrasias (IgM, IgG, IgA)
  - Leukemias
  - Lymphomas
  - Castleman's disease
- Solid organ malignancies – rare
  - Colon carcinoma
  - Renal cell carcinoma

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Table 24.5 Triggers and associations in acute hemorrhagic edema of infancy and urticarial vasculitis. NSAIDs, nonsteroidal anti-inflammatory drugs.
Fig. 24.8 Acute hemorrhagic edema of infancy. A, B Multiple edematous erythematous plaques on the face and extremities of a toddler. Some of the lesions have begun to become dusky.

Courtesy, Ilona J Frieden, MD.
Urticarial Vasculitis

Key Features

- Recurrent episodes of painful, persistent urticarial lesions that last >24 hours and often resolve with residual hyperpigmentation
- May occur with or without angioedema
- May be associated with constitutional symptoms and arthritis
Urticarial Vasculitis

Key Features (Cont.)

- Patients with hypocomplementemia are more likely to have systemic involvement
- Associated disorders include autoimmune connective tissue diseases (especially systemic lupus erythematosus, Sjögren’s syndrome) and viral infections
Fig. 24.9 Urticarial vasculitis. Several erythematous urticarial plaques on the foot and ankle.

Courtesy, Cora Whitney Hannon, MD, and Robert Swerlick, MD.
Erythema Elevatum Diutinum

Key Features

- Symmetric red-violet to red-brown papules and plaques
- Persistent lesions that develop on extensor surfaces
- Fibrosing leukocytoclastic vasculitis
Fig. 24.10 Erythema elevatum diutinum. A Erythematous papulonodules on the knee (acute lesions) admixed with resolving lesions. B Firm nodule on the dorsum of the hand in a patient with HIV infection (late-stage lesion).

A, Courtesy, Kenneth Greer, MD. B, Courtesy, Rachel Moore, MD.
Fig. 24.11 Erythema elevatum diutinum – histologic features. **A** An early-stage lesion, demonstrating a dense perivascular infiltrate of neutrophils admixed with lymphocytes and histiocytes. In addition, there is evidence of scattered nuclear dust and red blood cell extravasation. **B** A late-stage lesion, demonstrating a minimal inflammatory infiltrate and marked perivascular fibrous thickening. **Courtesy, Cora Whitney Hannon, MD, and Robert Swerlick, MD.**
Cryoglobulinemic Vasculitis

Key Features

- Palpable purpura, typically on the lower extremities
- Myalgias and arthralgias
- Associated with mixed serum cryoglobulins (IgM and IgG), most commonly in the setting of HCV infection
- Peripheral neuropathy and glomerulonephritis can develop
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Molecular composition</th>
<th>Associations</th>
<th>Pathophysiology</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Monoclonal IgM &gt; IgG&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Plasma cell dyscrasias, lymphoproliferative disorders</td>
<td>Vascular occlusion</td>
<td>Raynaud’s phenomenon, retiform purpura, gangrene, acrocyanosis</td>
</tr>
<tr>
<td>II&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Monoclonal IgM&lt;sup&gt;1&lt;/sup&gt; (&gt;IgG&lt;sup&gt;1&lt;/sup&gt;) against polyclonal IgG</td>
<td>HCV, HIV, autoimmune connective tissue diseases, lymphoproliferative disorders</td>
<td>Vasculitis</td>
<td>Palpable purpura, arthralgias, peripheral neuropathy, glomerulonephritis</td>
</tr>
<tr>
<td>III&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Polyclonal IgM&lt;sup&gt;1&lt;/sup&gt; against polyclonal IgG</td>
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</tbody>
</table>

<sup>*</sup>Referred to as “mixed” cryoglobulins because either monoclonal or polyclonal immunoglobulins bind to polyclonal immunoglobulins.

<sup>1</sup>Typically have rheumatoid factor activity (i.e. are directed against the Fc portion of IgG).

<sup>*</sup>Rarely IgA.

**Table 24.6 Classification of cryoglobulins.** HCV, hepatitis C virus; HIV, human immunodeficiency virus.

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Fig. 24.12 Cutaneous small vessel vasculitis due to mixed cryoglobulinemia. A The most common cause is hepatitis C viral infection. B Macular purpura mimicking Cullen's sign in a patient with hepatitis C infection.
Microscopic polyangiitis

Key Features

- Vasculitis of capillaries, venules and medium-sized arteries
- Palpable purpura, erythematous macules and patches, splinter hemorrhages and ulcers
- Constitutional symptoms, crescentic necrotizing glomerulonephritis and alveolar hemorrhage
- Presence of p-ANCA
- Absence of granuloma formation
Fig. 24.13 Microscopic polyangiitis. A Petechiae and multiple purpuric papules with central necrosis on the plantar surface. B Confluent hemorrhagic plaque on the medial and plantar aspect of the foot.

*Courtesy, Cora Whitney Hannon, MD, and Robert Swerlick, MD.*
Vasculitis: 2018
Clinical Features
Larger Vessel Vasculitis
Vasculitis: 2018
Histopathologic Features
Larger-Vessel Vasculitis
Granulomatosis with Polyangiitis (GPA)-Wegener’s Granulomatosis

Key Features

- Necrotizing granulomatous inflammation of the upper and lower respiratory tracts
- Pauci-immune glomerulonephritis
- Systemic vasculitis that can involve the skin and oral mucosa
Fig. 24.14 Wegener's granulomatosis. A Sharply demarcated ulcer on the distal lower extremity, sometimes misdiagnosed as pyoderma gangrenosum. B Ulceration of the tongue. C Subungual digital infarcts resembling splinter hemorrhages. D Palpable purpura of the distal lower extremity due to small vessel vasculitis (leukocytoclastic vasculitis).

A, Courtesy, Irwin Braverman, MD.
Eosinophilic Granulomatosis with Polyangiitis (EGPA) - Churg-Strauss Syndrome

Key Features

- Asthma and allergic rhinitis typically precede vasculitic phase
- Peak peripheral blood eosinophil count >10°/l
- Cutaneous vasculitis in approximately half of patients
- Histologic features consist of eosinophils, extravascular granulomas and vasculitis
Fig. 24.15 Churg–Strauss syndrome. A Palpable purpura of the buttocks due to small vessel vasculitis (leukocytoclastic vasculitis). B Purpuric dermal plaques of the palm that histologically demonstrated vasculitis of a small muscular artery. C Crusted, firm papules of the elbow.

C, Courtesy, Kalman Watsky, MD.
Polyarteritis Nodosa

Key Features

- Segmental vasculitis of predominantly medium-sized arteries
- Systemic and cutaneous variants both can present with palpable purpura, livedo racemosa, retiform purpura, ulcers, subcutaneous nodules or peripheral gangrene
Polyarteritis Nodosa

Key Features (Cont.)

- Extracutaneous manifestations of the systemic variant include fever, arthralgias, myalgias, paresthesias, abdominal pain, orchitis and renovascular hypertension.

- The cutaneous variant has a chronic, more benign course; it may be accompanied by mild systemic symptoms (fever, myalgias, arthralgias and peripheral neuropathy).
Fig. 24.16 Polyarteritis nodosa (PAN). A Retiform purpura of the dorsal foot in a patient with systemic PAN. B, C Livedo reticularis of the abdomen and lower extremities with multiple small “punched-out” ulcers in an adolescent with cutaneous PAN. This entity can overlap with the PAN-like syndrome with anti-phosphatidylserine-prothrombin complex antibodies that responds to anticoagulation.

B, C, Courtesy, Julie V Schaffer, MD.
Fig. 24.17 Cutaneous polyarteritis nodosa—histologic features. Mediumsized vessel vasculitis with neutrophilic debris, fibrin and red blood cells within the arteriolar wall situated at the junction of the reticular dermis and fat.

Courtesy, Thomas Horn, MD.
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/pericardium
  - 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.

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<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>
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<td>Discontinue immunosuppressants</td>
<td>2*</td>
<td>Colchicine (6-12 mg bid-tid)</td>
<td>2*</td>
<td>AZA (4-6 mg/day)</td>
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<td>MTX</td>
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<td>Treat underlying infections</td>
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<td>DMARDs</td>
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<td>Methylprednisolone</td>
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<td>CS + CYC</td>
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<td>CS + MTX</td>
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<td>CS + MTX</td>
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<td>Mycophenolate mofetil</td>
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<td>(to induce remission in limited disease)</td>
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<td>Mycophenolate mofetil</td>
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<td>CS + CYC + PEX</td>
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<td>(if severe renal disease, may be first line)</td>
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<td>Wegener's granulomatosis</td>
<td>CS + CYC</td>
<td>3</td>
<td>CS + CYC + PEX</td>
<td>3</td>
<td>Mycophenolate mofetil</td>
<td>3 *</td>
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<td>(to maintain remission)</td>
<td></td>
<td></td>
<td>(if severe renal disease, may be first line)</td>
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<tr>
<td>Churg–Strauss syndrome</td>
<td>CS</td>
<td>2</td>
<td>CS + CYC (first line in severe disease)</td>
<td>3</td>
<td>Mycophenolate mofetil</td>
<td>3 *</td>
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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; IVlg, intravenous immunoglobulin; MTX, methotrexate; MYC, mycophenolate mofetil; NSAI, nonsteroidal anti-inflammatory drugs; PEX, plasmapheresis; TMP-SMX, trimethoprim-sulfamethoxazole. Key references for treatment are summarized. References cited in this table (*) are available in the online content.
Vasculitis: Update 2018
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 2018 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:
Therapeutic Ladder -2018 More Severe Diseases

- Prednisone alone or in combination
- Pulse Prednisone
- Azathioprine
- Cyclophosphamide; pulse or daily
- Mycophenolate mofetil
- Chlorambucil
- Cyclosporine
- TNF alpha inhibitors
- Leflunomide
- Rituximab
- Countless treatments aimed at underlying diseases