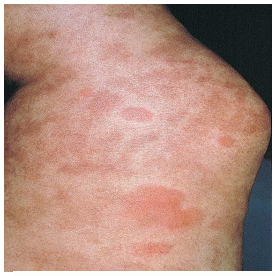

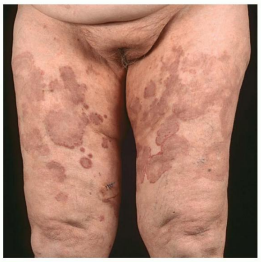

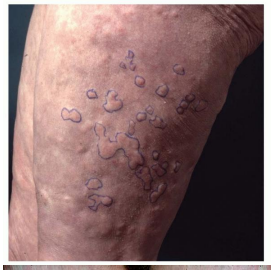

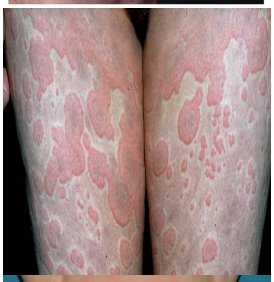

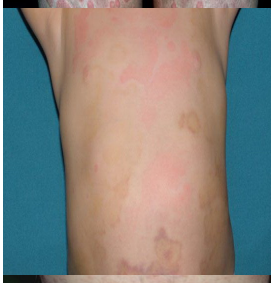

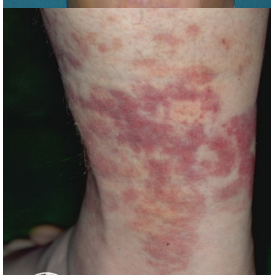

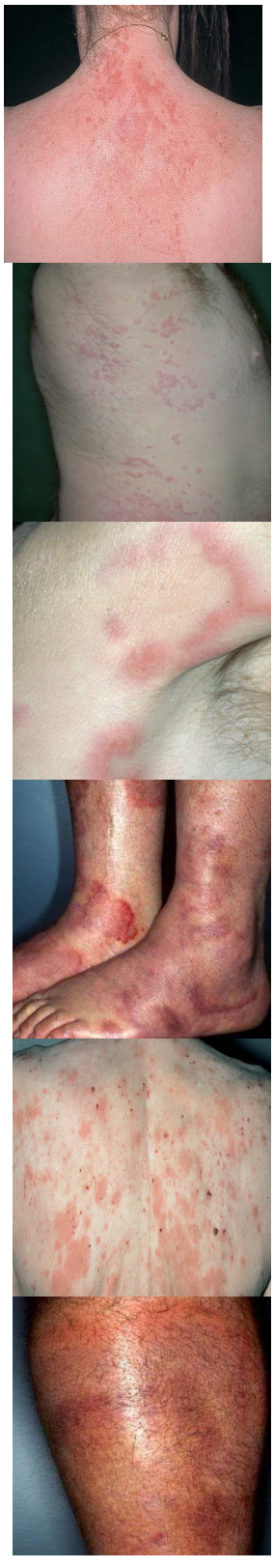

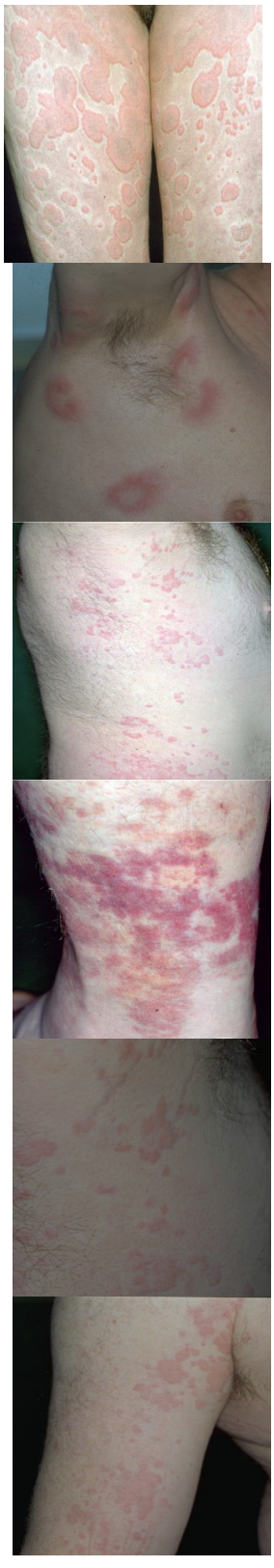

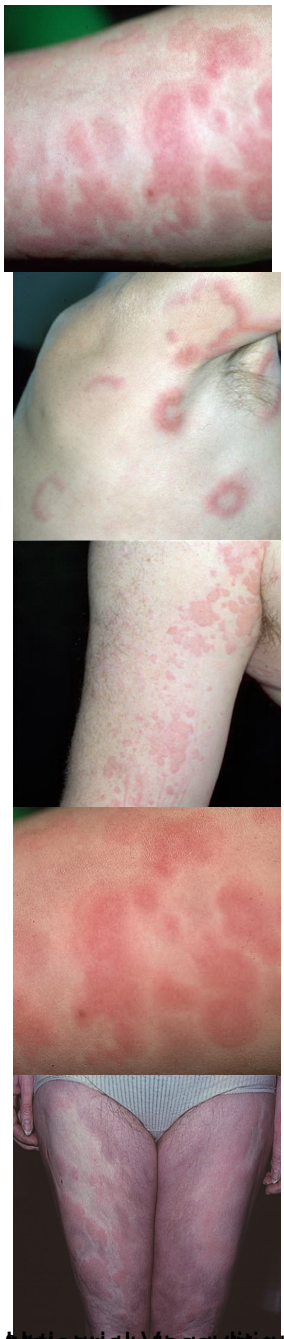

Pathophysiology

The pathophysiology of urticarial vasculitis is similar to other forms of cutaneous small vessel leukocytoclastic vasculitis. Urticarial vasculitis is a type III hypersensitivity reaction in which antigen-antibody complexes are deposited in the vascular lumina. This reaction results in complement activation and chemotaxis of neutrophils. These cells release various proteolytic enzymes, such as collagenase and elastase, resulting in damage to the vascular lumina. Some authors have speculated that eosinophils may be involved in the early stages of the vasculitic lesions. Patients with hypocomplementemic urticarial vasculitis are more likely to show autoantibodies to C1q and vascular endothelial cells.[5,6] The presence of antineutrophilic cytoplasmic antibodies is rare.

History

Patients with urticarial vasculitis present with an urticarial eruption, often accompanied by a painful or burning sensation. Lesions are generalized wheals or erythematous plaques, occasionally with central clearing, lasting for more than 24 hours in a fixed location (in contrast to urticaria, which resolves in minutes to hours or migrates continually). Petechiae may be noted within the lesions, and they may resolve with ecchymoses or postinflammatory hyperpigmentation. Patients may have photosensitivity, lymphadenopathy, arthralgia, angioedema (40%), fever, abdominal pain, dyspnea, and pleural and pericardial effusions.[4] Mos t cases of urticarial vasculitis are idiopathic.

The primary causes of urticarial vasculitis are as follows:

- Drug induced, such as ACE inhibitors, penicillin, sulfonamides, fluoxetine, cimetidine, diltiazem, thiazides, potassium iodide, non-steroid inflammatory drugs, and glatiramer acetate.[7]

- Rheumatic disease, such as SLE and Sjögren syndrome: Urticarial vasculitis has also been reported with immunoglobulin A and immunoglobulin M monoclonal gammopathies, mixed cryoglobulins, and hematologic and solid malignancies.[8]
- Viral disease, such as hepatitis B, hepatitis C,[9] and infectious mononucleosis

Urticarial vasculitis is divided into hypocomplementemic and normocomplementemic categories, as follows[10] :

- Hypocomplementemia often is associated with a systemic condition, such as SLE (in which >50% of patients have hypocomplementemia).[3] In addition, as many as 71% of patients with hypocomplementemic urticarial vasculitis have a positive antinuclear antibody titer but do not fulfill the American Rheumatism Association criteria for SLE.[5]

Some authors have suggested evaluation of hypocomplementemic urticarial vasculitis for immunoglobulin G antibodies to C1q. Individuals with these antibodies have a higher incidence of angioedema, ocular inflammation, glomerulonephritis, and obstructive pulmonary disease.

- Normocomplementemic vasculitis can be associated with connective-tissue disease but at a much lower rate.

Physical

Lesions of urticarial vasculitis initially appear as erythematous wheals (see image below). As the lesions progress, purpura may develop. Often, the urticarial vasculitis lesions resolve with postinflammatory pigmentation. Annular or targetoid lesions may be observed.

Causes

The etiology of urticarial vasculitis has not been elucidated. Associated conditions are listed in History.

Laboratory Studies

Check CH50, C3, C4, Clq, and antibodies to Clq in urticarial vasculitis patients. If these test results are positive, evaluate renal function and urinalysis to check for the effects of vasculitis on the kidneys.

If the history suggests viral infections, obtain hepatitis B, hepatitis C, and heterophile antibody

serologies.

Direct immunofluorescence may show deposition of vascular C3, fibrin, and immunoglobulins. A lupus band may be detected in patients with underlying lupus erythematosus.

If warranted, obtain antinuclear antibody and lupus serologies. Anti-SSA and anti-SSB may be seen in patients with Sjögren syndrome. Test results for antineutrophilic cytoplasmic antibodies are generally negative, and, if they are positive, the possibility of Wegener granulomatosis or microscopic polyangiitis should be considered.

Imaging Studies

Obtain chest x-ray films for urticarial vasculitis patients with hypocomplementemia and pulmonary symptoms.

Other Tests

If the patient is hypocomplementemic and has pulmonary symptoms, consider ordering pulmonary function tests.

Procedures

Perform skin biopsy to confirm the diagnosis of urticarial vasculitis. Recent lesions, less than 48 hours in onset, are the best for biopsy. Biopsy of a lesion of less than 24 hours' duration is best for direct immunofluorescence.

Histologic Findings

On biopsy, histologic findings are those of a leukocytoclastic vasculitis, defined as damage to the small vessels in the papillary and reticular dermis

Early lesions show a perivascular neutrophilic infiltrate involving postcapillary venules. Leukocytoclasis is present, expansion of the vessel wall occurs, and the endothelium is intact. Eosinophils may be noted early. Fibrin deposition and extravasation of red blood cells ensue.

Later in the lesion's course, infiltrate may become a mixture of lymphocytes and neutrophils. Consider performing direct immunofluorescence on the skin biopsy, which may show deposition of complement and fibrin in the blood vessels and, occasionally, immunoglobulin M, immunoglobulin G, and immunoglobulin A along the basement membrane zone of the skin.

Medical Care

Urticarial vasculitis tends to run a chronic course. Mortality is low, unless renal or pulmonary disease occurs. The goal of treatment is to achieve long-term control with the least amount of toxicity.

A complete patient history is the basis for treatment. In the history, ask for time of onset of the lesions; duration of the lesions (eg, >24 h); whether lesions are painful or burning, rather than pruritic; and the history of resolution with purpura or hyperpigmentation. Inquire about the patient's medications, fever, arthralgia, dyspnea, abdominal pain, and symptoms of angioedema.

Consultations

Consultation with the following specialists may be needed:

- Dermatologist: Skin biopsy is evaluated by a dermatologist/dermatopathologist to confirm the diagnosis.
- Rheumatologist: Consult a rheumatologist when SLE is suspected or if the patient has the hypocomplementemic variant with systemic symptoms.
- Allergist/immunologist: A guideline summary from the American Academy of Allergy, Asthma and Immunology, Consultation and referral guidelines citing the evidence: how the allergist-immunologist can help, may be helpful. [12]

Medication

Treatment of urticarial vasculitis is based on systemic effects of the disease, extent of cutaneous involvement, and previous response to treatment. For patients with cutaneous involvement only, antihistamines or nonsteroidal anti-inflammatory drugs (NSAIDs) may provide symptomatic relief. If these agents fail, colchicine, hydroxychloroquine, or dapsone may be effective. If all other treatment modalities have failed or if the patient has systemic involvement, consider initiating treatment with glucocorticoids. If the patient requires long-term treatment with

corticosteroids, consider every-other-day dosing of the steroid or the addition of azathioprine as a steroid-reducing agent. Response to newer agents, including mycophenolate mofetil[13,14] and rituximab, has been reported in the literature. However, larger studies have not been performed with these agents.

Antihistamines

May serve as an adjunctive agent to relieve the itching or burning associated with urticarial vasculitis. Given alone, they usually provide only symptomatic relief.

Hydroxyzine (Atarax, Vistaril)

Antagonizes H1 receptors in periphery. May suppress histamine activity in subcortical region of CNS. Can be used for symptomatic control. The recommended antihistamine for pregnant patients is diphenhydramine. Has been used safely in children.

-

Adult

0.5 mg/kg PO q6h or 25-100 mg PO qd/qid; not to exceed 50 mg PO q6h

Pediatric

0.5-0.6 mg/kg/dose PO q6h

-

CNS depression may increase with alcohol or other CNS depressants

-

Documented hypersensitivity

-

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Adverse effects include drowsiness, headache, dizziness, and nervousness; associated with clinical exacerbations of porphyria (may not be safe for porphyric patients); ECG abnormalities (alterations in T waves) may occur; may cause drowsiness

Diphenhydramine (Benadryl, Benylin, Diphen, AllerMax)

For symptomatic relief of symptoms caused by release of histamine in hypersensitivity reactions.
In pregnancy, use 25-50 mg PO q6h prn.

-

Adult

25-50 mg PO q6-8h prn; 10-50 mg IV/IM q6-8h prn; not to exceed 400 mg/d

Pediatric

5 mg/kg/d PO/IV/IM divided q6-8h; not to exceed 300 mg/d

-

Potentiates effect of CNS depressants; because of alcohol content, do not administer syrup form to patient taking medications that can cause disulfiramlike reactions

-

Documented hypersensitivity, MAOIs

-

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

May exacerbate angle-closure glaucoma, hyperthyroidism, peptic ulcer, and urinary tract obstruction

Anti-inflammatory agents

These agents modulate the immune system to reduce inflammation.

Colchicine

Alkaloid extract that inhibits microtubule formation. Often used for treatment of acute gout. Has been reported effective for urticarial vasculitis. Concentrates well in leukocytes and reduces neutrophilic chemotaxis and motility. Histologically, urticarial vasculitis presents with neutrophil involvement; therefore, colchicine possibly is useful. However, drug's effect has not been proven in clinical trials.

-

Adult

0.6 mg PO bid/tid

Pediatric

Children: Not established
Adolescents: 0.5 mg/kg PO divided bid/tid

-

Significantly increases sympathomimetic agent toxicity and effect of CNS depressants; may decrease vitamin B-12 absorption

-

Documented hypersensitivity; severe renal, hepatic, GI, or cardiac disorders; blood dyscrasias

-

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Diarrhea is common; severe hematologic adverse effects can occur; monitor CBC counts and creatinine levels; risk of renal failure, hepatic failure, permanent hair loss, bone marrow suppression, numbness or tingling in hands and feet, disseminated intravascular coagulopathy, and decreased sperm count

Sulfone antibiotics

Used for infectious diseases (eg, leprosy); however, sulfones are effective in inflammatory diseases. Mechanism of action may involve inhibiting free radical formation by neutrophils. In most case reports, these medications are effective only in purely cutaneous forms of urticarial vasculitis.

Dapsone (Avlosulfon)

Preferred sulfone. Other sulfones must be metabolized to dapsone for their effect. Mechanism of action is similar to that of sulfonamides in which competitive antagonists of PABA prevent formation of folic acid, inhibiting bacterial growth.
Dosing guidelines for dermatologic use have been well described in dermatitis herpetiformis. Most case reports about effect in urticarial vasculitis use dermatitis herpetiformis dosing guidelines. Has been used extensively in chronic bullous disease of childhood.

-

Adult

50 mg/d PO initial; can be increased by 50 mg/wk to 300 mg/d

Pediatric

1-2 mg/kg/d PO

-

Trimethoprim, probenecid, and folic acid antagonists (eg, pyrimethamine, MTX) may increase levels; activated charcoal, PABA, and rifampin may decrease levels; sulfonamides and hydroxychloroquine may increase hemolysis risk

-

Absolute: Documented hypersensitivity
Relative: G-6-PD deficiency (especially in African Americans, persons of Middle Eastern heritage, and Asians); significant cardiopulmonary disease; significant hematologic disease; sulfa allergy (cautious use in patients with sulfa allergy may be attempted; cross-reactivity is relatively rare and mild; do not use if previous reaction to sulfa was anaphylactic)

-

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Dose-related hemolytic anemia in all persons receiving dapsone to some degree; older RBCs more susceptible; most patients have 2g/dL drop in hemoglobin, with re-equilibration at 1g/dL below normal; reticulocyte count may be used to monitor bounce-back ability; patients with G-6-PD deficiency more affected
Dose-related methemoglobinemia may occur; degree of cyanosis not predictive of degree of methemoglobinemia; Patients with significant cardiopulmonary disease or low baseline hemoglobin levels may not be able to tolerate low levels of methemoglobin; vitamin E 800 IU/d and cimetidine 400 mg tid shown to provide a small amount of protection from formation of methemoglobin or hemolysis
Agranulocytosis may occur (1 in 240-425), is idiosyncratic, and mechanism not known; has occurred as early as 3 wk; All cases developed within 12 wk; fever, pharyngitis, and sepsis reported, with mortality rate of 50%; if discovered promptly, recovery occurs in 7-14 d; granulocyte colony-stimulating factor may speed recovery
Distal motor neuropathy with some sensory involvement may occur; distal motor weakness of hands and legs and wasting of hand muscles; most patients recover completely with discontinuance but recovery can take 2 wk to 2 y; mechanism of neuropathy unknown
Permanent retinal damage reported with overdosage; thought to be due to hypoxia
Acute psychosis may occur but usually only in leprosy patients
GI upset minimized if taken with food; primary hepatocellular hepatitis, cholestatic hepatitis, hypoalbuminemia, gall bladder perforation, pancreatitis may occur
Dapsone hypersensitivity syndrome is mononucleosislike eruption with fever; skin eruption has ranged from maculopapular to TEN; hepatitis; peripheral eosinophilia; fatalities reported; treatment with steroids have been tried but due to its rarity, success unproven
Cutaneous hypersensitivity eruptions may include maculopapular, EM or TEN (rare); photosensitivity may occur; animal studies (not human) have shown slight increase in malignancies if taken for 2 y or longer

Antimalarials

Like other medications used to treat urticarial vasculitis, antimalarials are believed to exert their effect by their anti-inflammatory properties. Antimalarials reduce neutrophilic chemotaxis. In addition, they increase pH in lysosomes, which may affect antigen presentation. This class of medications usually is effective only in cutaneous disease.

Hydroxychloroquine (Plaquenil)

Preferred antimalarial agent because of its low toxicity and high effectiveness profile. Usually

well tolerated if carefully monitored by prescribing physician. Therapy is required for 4-8 weeks before evaluating effectiveness.

-

Adult

6.5 mg/kg PO or 400 mg/d PO, whichever is less

Pediatric

3-5 mg/kg/d PO divided bid; not to exceed 400 mg/d

-

Serum levels increase with cimetidine; magnesium trisilicate may decrease absorption; may increase digoxin levels; do not give with chloroquine due to increased retinal toxicity

-

Absolute: Documented hypersensitivity; retinopathy from any cause
Relative: Pregnancy or breastfeeding; retinal or visual-field changes; severe blood dyscrasias; psoriasis; G-6-PD deficiency (caution advocated, but routine G-6-PD screening not recommended; associated with hemolysis, but not in usual dosage range); significant hepatic dysfunction; myasthenia gravis, significant neurologic disease; long-term therapy in children (listed in *Physicians Desk Reference* as contraindication for hydroxychloroquine; main concern is overdose/toxicity; chronic toxicity risk, however, thought to be no greater than in adults); neither drug available as a syrup; crush tab and mask bitter taste in jam, applesauce, or other soft food

-

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may

use if benefits outweigh risk to fetus

Precautions

Hepatic disease, G-6-PD deficiency, psoriasis, and porphyria; not recommended for long-term use in children; perform periodic (6 mo) ophthalmologic examinations; test periodically for muscle weakness

Nonsteroidal anti-inflammatory agents

Most commonly used for relief of mild to moderate pain. The basis behind the use of indomethacin is empiric. It was used with some effectiveness on the cutaneous manifestations of the disease in several case reports.

Indomethacin (Indocin)

Only NSAID reported effective in urticarial vasculitis. Rapidly absorbed; metabolism occurs in liver by demethylation, deacetylation, and glucuronide conjugation; inhibits prostaglandin synthesis.

-

Adult

100-150 mg/d PO in divided doses.

Pediatric

1-2 mg/kg/d PO in 2-4 divided doses; not to exceed 150-200 mg/d.

-

Coadministration with aspirin increases risk of serious NSAID-related adverse effects; may decrease effects of beta-blockers, hydralazine, and captopril; may decrease diuretic effects of furosemide and thiazides; coadministration with anticoagulants may prolong PT (monitor bleeding); may increase risk of MTX toxicity, which can manifest as stomatitis, bone marrow

suppression, or nephrotoxicity; coadministration may increase phenytoin levels; probenecid may increase toxicity of NSAIDs

-

Documented hypersensitivity; avoid in GI bleeding or renal insufficiency.

-

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

In late pregnancy, as with other NSAIDs, indomethacin should be avoided because it may cause premature closure of the ductus arteriosus; acute renal insufficiency, hyperkalemia, hyponatremia, interstitial nephritis, and renal papillary necrosis may occur; increases risk of acute renal failure in patients with preexisting renal disease or compromised renal perfusion; reversible leukopenia may occur (discontinue in persistent leukopenia, granulocytopenia, or thrombocytopenia)

Cytotoxic agents

Azathioprine may be used as a steroid-sparing agent once other therapeutic options have been exhausted. Measurement of thiopurine methyltransferase can help ensure safe and optimal treatment with azathioprine.

Azathioprine (Imuran)

Purine precursor that affects formation of adenine and guanine. Results in impaired DNA synthesis in immunocompetent cells such as lymphocytes, which are dividing rapidly during inflammatory process. Has slow onset of action; rarely used as monotherapy.

-

Adult

1 mg/kg/d qd/bid (empiric) or based on TPMT level (see Precautions); increase dose by 0.5 mg/kg/d after 6-8 wk if necessary; increase q4wk; 2 mg/kg/d maximum dose for most dermatologic purposes

Pediatric

Not established

-

Toxicity increases with allopurinol; concurrent use with ACE inhibitors may induce severe leukopenia; may increase levels of methotrexate metabolites; may decrease effects of anticoagulants, neuromuscular blockers, and cyclosporine

-

Absolute: Allergy to azathioprine, pregnancy or attempting pregnancy, clinically significant active infection
Relative: Concurrent use of allopurinol, prior treatment with alkylating agents (cyclophosphamide, chlorambucil, melphalan, others) because of high risk of neoplasia; pediatric patients (safety and efficacy in pediatric population not established)

-

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

TPMT testing is not entirely reliable; involves testing TPMT activity in RBCs, which correlates with systemic TPMT activity; functional enzyme test has been shown to have variability between test sites, and kits may contain varying amounts of enzyme inhibitor; starting at low doses,

monitoring for pancytopenia, and then increasing dose is alternative; if clinical response is not good, patient may be a homozygote for high activity and may need an increased dose
Possible increased risk of lymphoproliferative disorders with long-term therapy; increases risk of neoplasia; caution with liver disease and renal impairment; hematologic toxicities may occur
Dosing by TPMT level
TPMT <5 U: No treatment with azathioprine
TPMT 5-13.7 U: Up to 0.5 mg/kg/d
TPMT 13.7-19 U: Up to 1.5 mg/kg/d
TPMT >19 U: Up to 2.5 mg/kg/d

Glucocorticoids

Often the treatment of choice. However, given their long-term adverse effect profiles, they are used only for significant cutaneous disease or systemic involvement. For long-term treatment, combination of prednisone and another medication may be required.

Prednisone (Deltasone)

Although is most effective, adverse effect profiles preclude it from use as a first-line agent. Consider only after failure of antihistamines, indomethacin, colchicine, dapsone, or hydroxychloroquine. Effect on urticarial vasculitis likely is mediated by its anti-inflammatory effect. This class of medications decreases capillary permeability and inhibits the mitotic rate of lymphocytes.

-

Adult

0.5-1.5 mg/kg/d PO initial; taper as disease responds; if chronic use required, qod administration is safer

Pediatric

0.5-2 mg/kg/d PO in divided dose bid to qid

Increased steroid levels: Ketoconazole, erythromycin, clarithromycin, estrogens, and birth control pills increase levels; aminoglutethimide, phenytoin, and phenobarbital decrease levels
Levels of potassium-depleting diuretics (potentiates potassium loss and digitalis toxicity) and cyclosporine may increase; levels of isoniazid, insulin (resistance is induced), and salicylates may decrease
Monitor anticoagulant therapy and theophylline levels

-

Absolute: Systemic fungal infection; herpes simplex keratitis; hypersensitivity (usually with corticotropin, occasionally noted with IV preparations)
Relative: Hypertension, active tuberculosis, congestive heart failure, prior psychosis, positive IPPD result, glaucoma, severe depression, diabetes, active peptic ulcer disease, cataracts, osteoporosis, recent bowel anastomosis, pregnancy

-

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections may occur with glucocorticoid use; use lower dose in hypothyroidism, liver disease, and obesity (cortisol-binding globulin level is decreased, which increases free fraction of steroid); pregnancy, hyperthyroidism, and concurrent estrogen therapy may increase cortisol-binding globulin level