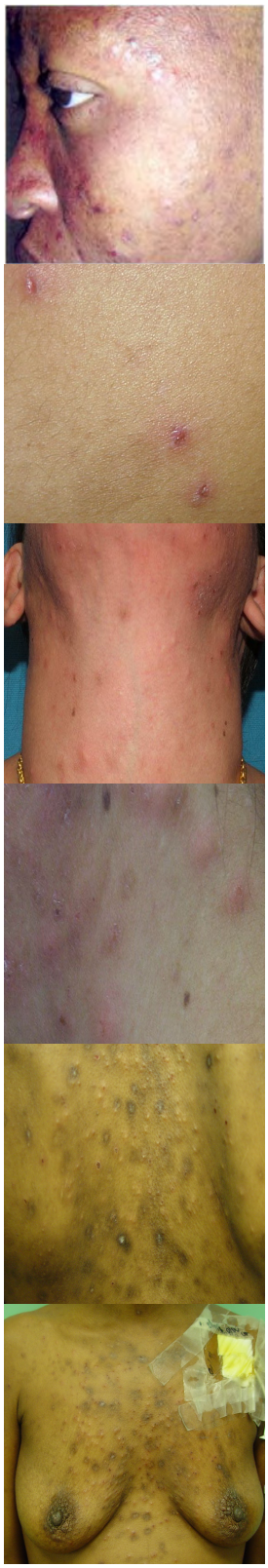

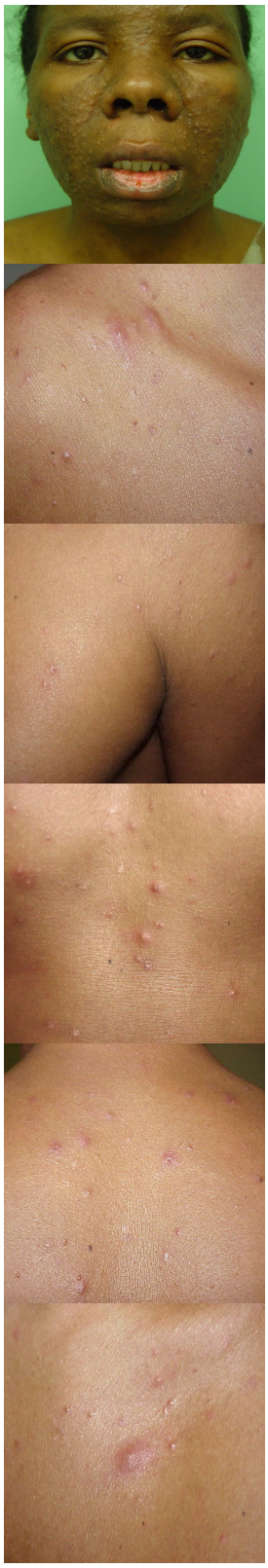

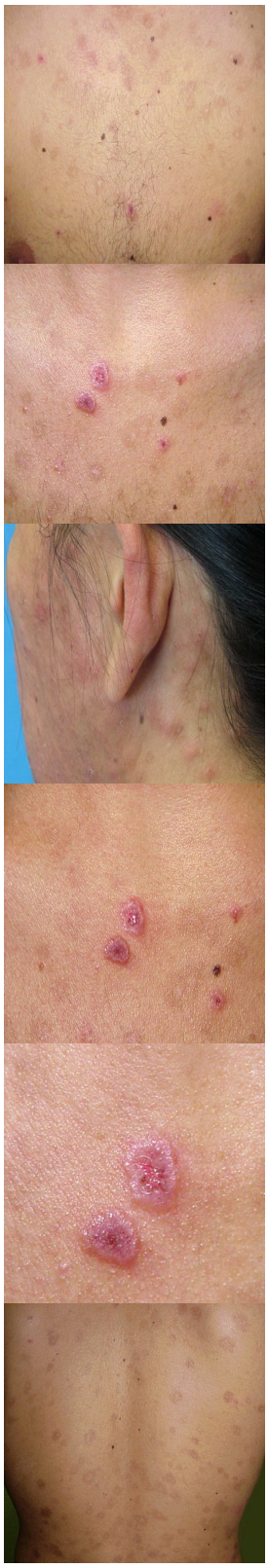

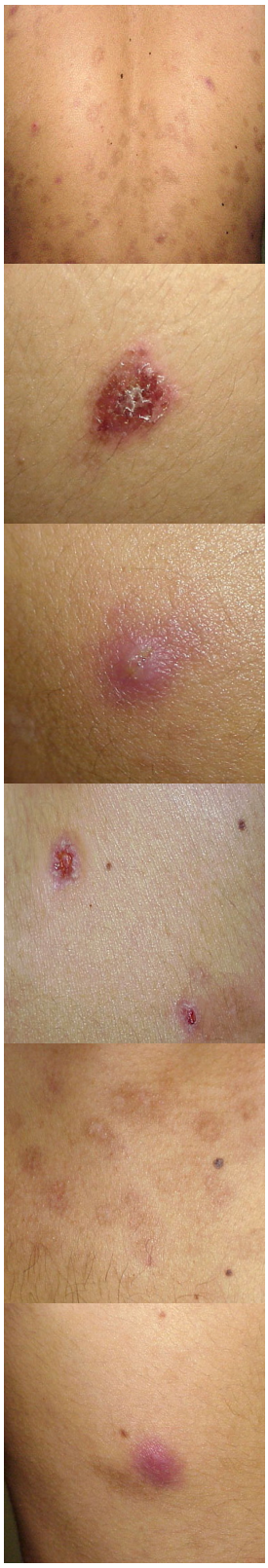

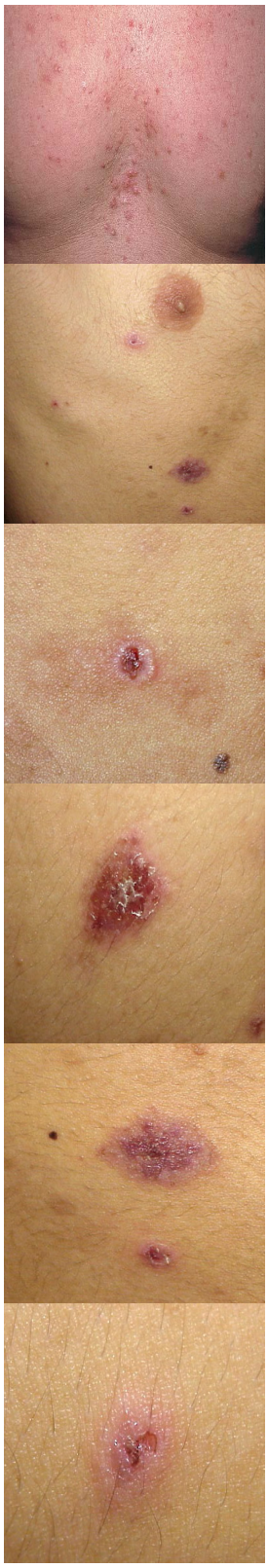

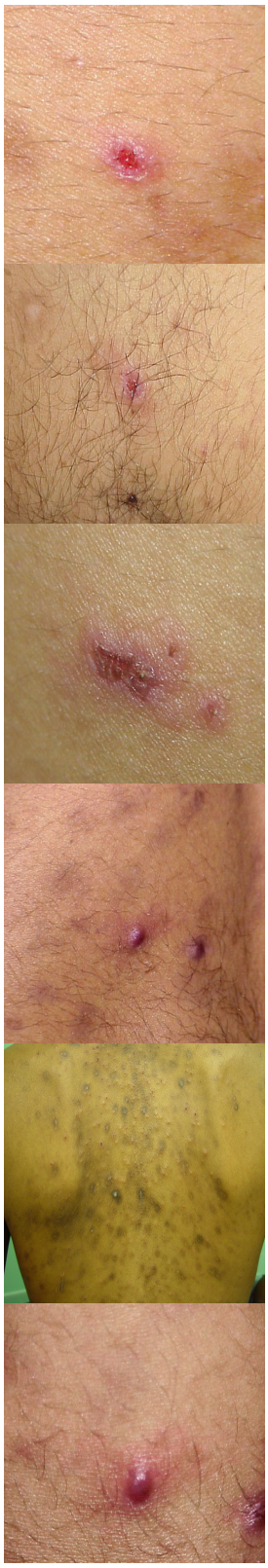

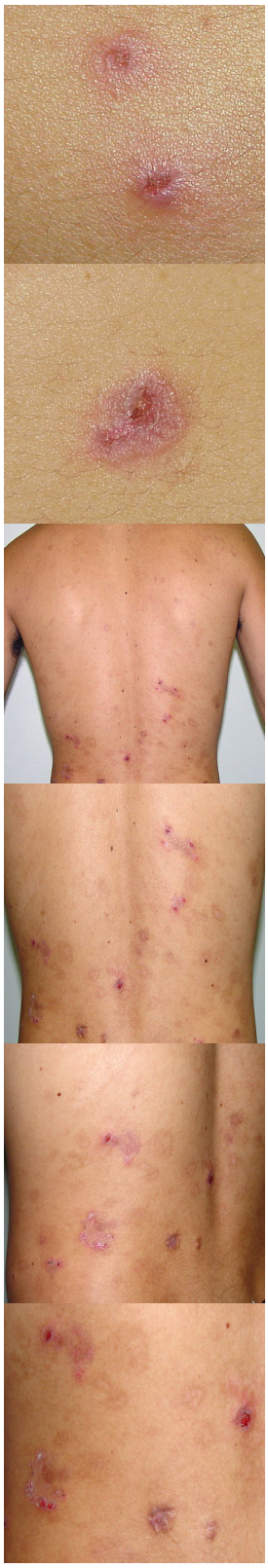

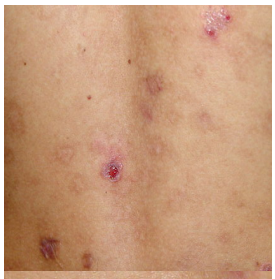
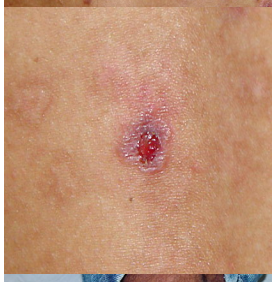
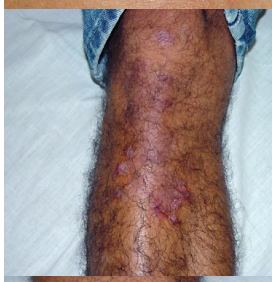
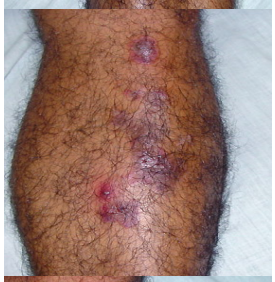
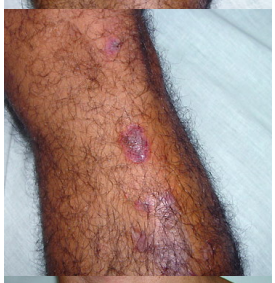
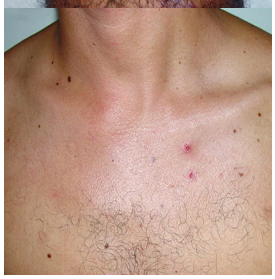

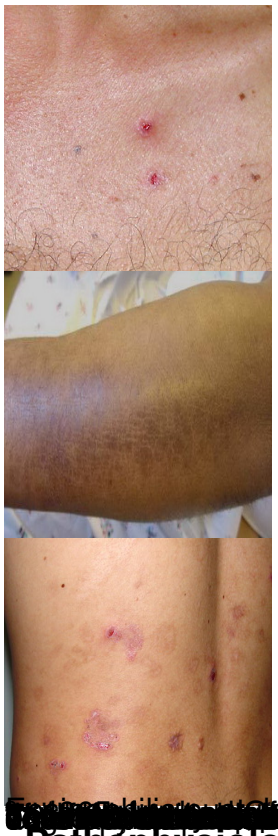

Pathophysiology

A histologic resemblance exists between eosinophilic pustular folliculitis and fungal folliculitis. Some investigators have speculated that eosinophilic pustular folliculitis is due to hyperreactivity to dermatophytes or saprophytic fungi, such as *Pityrosporum ovale,* in association with a disordered immune system. This concept is supported by the favorable therapeutic response of some patients to oral itraconazole therapy.

The follicle mite, *Demodex,* has also been considered a possible triggering agent. In certain patients, a combination of *Pityrosporum* species and *Demodex* species might play a role in the pathogenesis of the disease. An aberrant helper T-cell type 2 immune response to a follicular antigen, such as *Demodex,* might be involved in the pathogenesis of HIV-associated eosinophilic pustular folliculitis (see the image below). Eosinophilic pustular folliculitis has been described in atopic children with hypersensitivity to *Dermatophagoides pteronyssinus.*

An anaerobic organism similar in morphology to *Leptotrichia buccalis* has been found in one biopsy specimen of a patient with HIV-associated Ofuji disease; the disease responded to oral metronidazole. Others believe that at least the HIV-associated form is an autoimmune disorder with the sebaceous gland cell or a constituent of sebum serving as an autoantigen.

A single case has been reported of a patient with Ofuji disease with pemphiguslike antibody detected by direct immunofluorescence on both lesional skin and healthy skin and by indirect immunofluorescence on human skin but not on guinea pig esophagus.[4] Yet another patient with Ofuji disease and high titers of circulating immunoglobulin G and immunoglobulin M antibodies to the cytoplasm of the basal cells of the epidermis and the outer sheath of hair follicles has also been described. [5]

Another theory is that eosinophilic chemotactic factors from skin surface lipids may be involved. [6]

A selective migration of leukocyte factor antigen-1–positive eosinophils and lymphocytes to hair follicles may be explained by intercellular adhesion molecule-1 expression by keratinocytes on follicular epithelium but not on epidermis. The expression of endothelial-leukocyte adhesion molecule-1 and vascular cell adhesion molecule-1 by vascular endothelium around hair follicles may also explain this migration.

Eosinophils infiltrating into the dermis and the follicular epidermis express neuronal nitric oxide synthase.[7] Activated eosinophils release major basic protein with subsequent tissue damage. In addition to degranulating eosinophils, degranulating mast cells are present in the skin of most patients with HIV-associated eosinophilic folliculitis, which suggests a role for both of these cell types in the pathogenesis of this disease.

History

- The distribution tends to be a seborrheic one on the head and the trunk. About a fifth of patients have palmar and/or plantar plaques, which may be the first sign appearing weeks or months before other clinical features.
- Lesions are less commonly pruritic with the classic type than in the other 2 forms.

Physical

Patients with eosinophilic pustular folliculitis in the classic form have chronically recurrent crops of sterile follicular papulopustules with peripheral extension and central clearing.[8,9]

- Papulopustules with or without plaques tend to favor the face and the trunk as shown below, although the extremities may also be involved. With the classic form, the palms and the soles may also be affected. In children, the scalp, particularly at the vertex, is most frequently involved

- Some patients may have features of coexistent Ofuji disease and eosinophilic lymphoid granuloma (Kimura disease). [10]
- Individual papulopustules may be larger in the classic form, up to 20-50 mm in diameter, rather than the 1-3 mm in diameter seen in patients with HIV disease and in infants; peripheral extension with central clearing may be much less frequent in these 2 forms than in the classic one, which often has an erythematous base. The latter tends to heal more commonly with postinflammatory hyperpigmentation.
- No systemic involvement is evident, although a peripheral leukocytosis and eosinophilia may be seen. Atypical features, such as nonfollicular papules and urticarial plaques, are often evident in patients with HIV disease and in infants.

Causes

The cause of eosinophilic pustular folliculitis is unknown. Possible etiologies are discussed in Pathophysiology. Reports have described Asian patients in whom eosinophilic pustular folliculitis seemed to be associated with silicone tissue augmentation[11] or autologous peripheral blood stem cell transplantation.
[12]

A middle-aged Japanese woman has been described in whom eosinophilic pustular folliculitis was induced by a combination of allopurinol and timepidium bromide as suggested by the results of an oral provocation test with both drugs.
[13]

Moreover, allopurinol alone seemed to induce generalized eosinophilic pustular folliculitis.
[1]

Laboratory Studies

- Cytologic smears show abundant eosinophils.
- In the classic form, mild-to-moderate leukocytosis and eosinophilia are often evident. The latter is seen in about one half of patients.
- With HIV disease, the CD4 count is often less than 300 cells/µL.
- Infants with this disorder may have an elevated serum immunoglobulin E level with reduced serum immunoglobulin G and immunoglobulin A levels and diminished neutrophil

chemotactic activity.

- Because childhood eosinophilic pustular folliculitis may be associated with AIDS, lymphoma, leukemia, and other hematologic diseases, a thorough systemic evaluation is indicated.
- Take skin swabs for microscopy and culture and scrapings for mycologic analysis when a microbial infection or superinfection is suspected.
- Consider HIV- and non–HIV-related causes of immunodeficiency.
- When vesicles predominate, perilesional skin may be examined with direct immunofluorescence, and serum may be evaluated with indirect immunofluorescence on healthy human skin and/or desmoglein 1/desmoglein 3 enzyme-linked immunosorbent assay to exclude pemphigus foliaceus or pemphigus vulgaris. Both of these conditions might initially be evident as pemphigus herpetiformis, thus looking like eosinophilic pustular folliculitis both clinically and histopathologically.

Histologic Findings

Examine fresh, unexcoriated papulovesicles histologically, ideally in serial sections. Transverse sectioning may be needed if routine vertical sections give equivocal results as depicted below. Use routine hematoxylin and eosin stain as well as special stains for fungi and bacteria.

Subcorneal pustules of predominately eosinophils may be evident in the epidermis and the outer root sheath of hair follicles. Hair and sebaceous gland structures may be infiltrated with eosinophils, plus a few neutrophils and mononuclear cells

A patchy sebaceous lysis is observed in certain cases of HIV-related eosinophilic pustular folliculitis. Follicular eosinophilic abscesses are infrequently observed in HIV-associated cases of Ofuji disease. Infantile eosinophilic pustular folliculitis of the scalp may show an interfollicular dermal infiltrate with a substantial admixture of eosinophils and flame figures but not follicular spongiosis or degeneration.

Sometimes, mucin deposition can be observed in the hair follicles. Histopathologic study may reveal the coexistence of Ofuji disease and follicular mucinosis in patients with or without concomitant HIV infection. The lymphocytes in the HIV-associated type are predominately $CD8^+$ lymphocytes.

Palmar and plantar plaques show subcorneal or intraepidermal eosinophilic abscesses and spongiosis. Small foci of acantholysis may be seen in individual cases of eosinophilic pustular folliculitis.

Medical Care

A variety of options have been described with variable results.

- In classic cases, common options for treatment include indomethacin (orally or topically)[15, 16] and its newer derivative acemetacin,[17] dapsone, topical and systemic steroids, isotretinoin, itraconazole, permethrin, interferon, and antibiotics.[18] The experience of Japanese dermatologists is that indomethacin is by far the most effective in the classic form, although the mode of its action in this disease is still poorly understood.

- Ultraviolet therapy with ultraviolet B or with ultraviolet A and psoralen plus ultraviolet A may be beneficial.[19,20] The authors tend to try topical itraconazole cream first in patients with HIV-associated disease, adding an oral sedating antihistamine for bedtime use if pruritus is severe. Cetirizine seems to be a favorite because of its preferential effect on eosinophils, although these authors often prefer 4 mg of cyproheptadine at bedtime.

- In patients with HIV-associated disease, antiretroviral therapy tends to greatly diminish or even eliminate the severity of this disorder.
- Some patients with HIV-associated Ofuji disease may respond to oral metronidazole.

Medication

Because the etiology and the pathogenesis of eosinophilic pustular folliculitis have not been fully elucidated, no established treatment schemes exist. A number of options have been tried with various results; however, no controlled treatment trials have been performed for this condition. Oral indomethacin consistently appears to be most beneficial, at least in the classic

form of the disease, whereas permethrin and cyproheptadine might alleviate the symptoms in some patients, especially in HIV-associated cases of the disease. The correction of immunodeficiency in HIV-related eosinophilic pustular folliculitis may clear the skin lesions. Systemic treatment modalities may not be needed for an infantile/childhood variant of eosinophilic pustular folliculitis because most cases respond to topical corticosteroids.

An alternative therapeutic option in patients with a long-term history of unsuccessful response to conservative therapy is ionizing radiation.[21] Reports have suggested that eosinophilic pustular folliculitis may respond to treatment with topical tacrolimus,
[22]

pimecrolimus,
[23]

or transdermal nicotine patches.
[24]

Additionally, one case report suggests that treatment with intravenous interferon gamma followed by oral ciclosporin may yield longer-lasting benefit by correcting an aberrant T-helper-2 – type immune response implicated in the pathogenesis of this dermatosis.
[25]

Nonsteroidal anti-inflammatory drugs

These agents inhibit inflammatory reactions and pain by decreasing activity of cyclooxygenase, which results in a decrease of prostaglandin synthesis.

Indomethacin (Indocin)

A potent inhibitor of cyclooxygenase, which may decrease the local production of arachidonic acid derived chemotactic factors for eosinophils present in sebum (eg, 12-L-hydroxy-5,8,10-heptadecatrienoic acid and/or prostaglandin).

Adult

50 mg PO pc tid; taper as symptoms resolve

Pediatric

Not established

Coadministration with aspirin increases risk of inducing serious NSAID-related adverse effects;

probenecid may increase concentrations and, possibly, toxicity of NSAIDs; may decrease effect of hydralazine, ACE inhibitors, and beta-blockers; may decrease diuretic effects of furosemide and thiazides; may increase PT when taking anticoagulants (instruct patients to watch for signs of bleeding); may increase risk of methotrexate and lithium toxicity; phenytoin levels may be increased when administered concurrently; concurrent administration with clopidogrel should be monitored closely for bleeding; coadministration with quinolones may increase risk of seizures

Documented hypersensitivity; GI bleeding or renal insufficiency; treatment of peri-operative pain in setting of coronary artery bypass graft; neonates with active bleeding, infection, necrotizing enterocolitis, severe renal failure, thrombocytopenia, or coagulation defects; patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs

Pregnancy

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

Precautions

Category D in third trimester of pregnancy (may cause closure of 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 if leukopenia, granulocytopenia, or thrombocytopenia persists)
Adverse effects include anemia, aplastic anemia, asthma , bronchospasm, blurred vision including corneal deposit and retinal disorder, inflammatory disorder of digestive tract including gastrointestinal perforation and ulcer, cardiac dysrhythmia, chest pain and myocardial infarction, congestive heart failure, cerebrovascular accident, epilepsy, hearing loss, hematuria, nephrotic syndrome, newborn renal dysfunction, dyspnea, edema, hypertension, and transitory neonatal hyperkalemia

Scabicides

These agents might be useful in some HIV-associated cases of eosinophilic pustular folliculitis in which the commensal hair follicle mite, *Demodex,* might be a triggering antigen; however, lesions reappear with discontinuation of treatment.

Permethrin (Elimite)

Acts on the nerve cell membrane to disrupt sodium channel current by which the polarization of the membrane is regulated. Delayed repolarization and paralysis of pests are the result.

Adult

Initial: Massage 5% cream or 1% liquid into affected skin qd
Maintenance: 1-2 applications/wk

Pediatric

<2 years: Not established
>2 years: Apply as in adults

None reported

Documented hypersensitivity to permethrin/chrysanthemums

Pregnancy

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

Precautions

May exacerbate pruritus, erythema, and edema temporarily; use in pregnancy only if clearly needed

Antihistamines

These agents may alleviate itching in some HIV-associated cases of eosinophilic pustular folliculitis. Sedating forms may be more effective (especially for nocturnal pruritus).

Cyproheptadine (Periactin)

For the symptomatic relief of allergic symptoms caused by histamine released in response to allergens and skin manifestations.

Adult

4 mg PO hs; not to exceed 0.5 mg/kg/d

Pediatric

<2 years: Not established
2-6 years: 2 mg PO hs; not to exceed 12 mg/d
>6-14 years: 4 mg PO bid/tid; 16 mg/d maximum
>14 years: Administer as in adults

MAOIs prolong and intensify the anticholinergic effects; may have additive effects with alcohol and other CNS depressants; as a serotonin antagonist, may oppose effects of agents that inhibit serotonin reuptake; may blunt thyrotropin response

Documented hypersensitivity; newborn or premature infants; breastfeeding; during MAOI therapy; in cases of angle-closure glaucoma; stenosing peptic ulcer; symptomatic prostatic hypertrophy; bladder neck obstruction; pyloroduodenal obstruction; elderly and/or debilitated patients

Pregnancy

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

Precautions

May diminish mental alertness; has an atropinelike action; caution in patients with a predisposition to urinary retention, history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, or hypertension; may thicken bronchial secretions caused by anticholinergic properties, and may inhibit expectoration and sinus drainage

Hydroxyzine (Atarax)

Antagonizes H1 receptors in periphery. May suppress histamine activity in subcortical region of CNS.

Adult

25-100 mg PO qd/qid

Pediatric

0.6 mg/kg/dose PO q6h