Pathogenesis

Immunologic: can involve Type I, II, III, IV hypersensitivity reactions.

Nonimmunologic: related to pharmacology of the drug, predictable, and dose dependent.

Route of administration: can be observed via oral, topical, and injectable administration or via inhalation.

Clinical Presentations

Erythema multiforme, toxic epidermal necrolysis, pemphigus foliaceus, vaccine reaction, cutaneous vasculitis, and lichenoid drug eruption.

Unique feline reactions: miliary dermatitis reaction, vaccine reaction—injection site fibrosarcomas.

Erythema Multiform

Involves drug-induced apoptosis, which is a form of programmed cell death.

Acute onset of lesions with erythematous macules, “target lesions,” urticarial plaques, vesicles and bullae, concurrent systemic illness (fever, depression, anorexia).

Mucous membrane involvement—vesicles, bullae, ulcers; so-called erythema multiforme major or Stevens-Johnson syndrome—can be life threatening.

Drugs Implicated

Aurothioglucose, Cephalexin, chloramphenicol, gentamicin, trimethoprim sulfas, ormetoprim sulfas, tetracycline, Diethylcarbamazine, levamisole, L-thyroxine, phenobarbital.

Toxic Epidermal Necrolysis

Severe erythema multiforme? Involves massive and sudden apoptosis.

Acute onset of lesions with a diffuse erythematous rash, vesicles and bullae, full thickness skin sloughing and ulcers. May affect footpads, mucous membranes. The lesions are usually painful.

Concurrent fever, anorexia, lethargy, depression are common features with secondary sepsis a problem. Often a fatal disease.

Drugs Implicated

Penicillins, cephalosporins, trimethoprim sulfas, Griseofulvin, Levamisole, 5-fluorocytosine, topical flea dips (D-limonene).

Drug-Induced Pemphigus

Mimics pemphigus foliaceus.

Acute, transient pustular eruptions, with the subsequent formation of crusts, scales, erosions, and epidermal collarettes. Variable distribution patterns, and systemic illness is rare.
**Drugs Implicated**

Ampicillin, cephalosporins, sulfonamides, Diethylcarbamazine, thiabendazole, Cimetidine, procainamide.

**Vaccine Reactions**

Most commonly observed at site of a subQ or IM vaccination using rabies, and DHLP-parvo vaccines. Can occur from weeks to months post-vaccination with the development of a subsequent focal area of alopecia and hyperpigmentation.

**Breed Predisposition**

Poodle, bichon frise, shih tzu, lhasa apso, miniature schnauzer, Yorkshire terrier, Bedlington terrier, silky terrier.

Most spontaneously resolve over several months. Esion may remain static or the area of alopecia and hyperpigmentation can gradually enlarge over months to years.

**Treatment**

Tincture of time in most cases. Surgical excision is recommended if the lesion has remained static for more than 6 months and is excisable.

Pentoxifylline (Trental)—15 mg/kg TID x 3 months.

**Cutaneous Vasculitis**

Acute onset of palpable purpura, hemorrhagic bullae, crateriform ulcers, full thickness skin sloughing, acrocyanosis of distal extremities, large areas of erythematous or purplish skin that does not blanch on diascopy. Lesion often painful, and there may be pitting edema of distal extremities. Concurrent systemic illness is common with anorexia, depression, and fever.

**Drugs Implicated**

Penicillins, sulfonamides, cephalosporins, dexamethasone, DHLP-parvo vaccine.

**Lichenoid Drug Eruption**

Solitary to multiple papillomatous or plaque-like lesions

**Drugs Implicated**

Cyclosporine (Atopica, Neoral, Gengraf).

**Feline Miliary Dermatitis Reaction**

Miliary lesions that affect head, face, and neck regions with intense pruritus. Mimics “food allergy.”

**Drugs Implicated**

Methimazole (Tapazol), Propranolol.
**Feline Vaccine Reaction**

*Injection Site Fibrosarcomas*

Interscapular and femoral regions, associated with either subQ or IM injections. Tumor may develop 1–2 years post-vaccination.

*Vaccines Implicated*

FeLV, rabies, FVRCP.

**Diagnosis of Cutaneous Drug Reactions**

*History*

Observed reaction does not resemble pharmacological action. Prior exposure to drug may have been well tolerated. The reaction can be reproduced by small amounts of drug, the reaction is consistent with a known hypersensitivity response and usually occurs within several days of drug exposure, and the lesions usually resolve within several days of drug withdrawal.

*Drug Rechallenge*

Proves cause and effect relationship. However, the clinical signs are often more severe upon subsequent exposure, and the outcome can be fatal.

**Erythema Multiforme**

*Histopathology*

Hydropic interface dermatitis, dyskeratotic keratinocytes with satellitosis, superficial perivascular infiltrates with mononuclear cells.

**Toxic Epidermal Necrolysis**

*Histopathology*

Hydropic degeneration of basal cells, Coagulation necrosis of epidermis, absence of dermal inflammation, dermoeipidermal separation, and bullae formation.

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<thead>
<tr>
<th>CLINICAL CRITERIA</th>
<th>EMm</th>
<th>EMM</th>
<th>SJS</th>
<th>OVE</th>
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<tbody>
<tr>
<td>Flat or raised, focal or multifocal, target lesions</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Number of mucosa involved</td>
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<tr>
<td>Erythematous or purpuric, macular or patchy eruption</td>
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<td>&lt;50%</td>
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<tr>
<td>Epidermal detachment</td>
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<td>&lt;10%</td>
<td>&lt;10%</td>
<td>10-30</td>
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**Pemphigus Foliaceus**

*Histopathology*

Subcorneal pustules, acantholytic cells, neutrophils, eosinophils, and involvement of hair follicles.

**Vaccine Reaction**

*Histopathology*

Vasculitis, panniculitis, dermal edema, atrophic hair follicles, hydropic degeneration of basal cells.

**Cutaneous Vasculitis**

*Histopathology*

Most commonly leukocytoclastic, neutrophils in vessel walls, “nuclear dust,” fibrinoid degeneration, thrombi, perivascular hemorrhage, and edema.

**Lichenoid Drug Eruption**

*Histopathology*

Psoriasiform lichenoid dermatosis—with or without papillomavirus.

**Unique Feline Reactions**

**Miliary Dermatitis**

*Histopathology*

Epidermal crusts, spongiosis, neutrophilic and eosinophilic vesicopustules, eosinophilic perivascular infiltrates.

**Vaccine Reactions**

*Histopathology*

Fibrosarcoma.

**Treatment**

Discontinue suspected drug and avoid chemically related or similar drugs. When multiple drugs are present, all should be discontinued. Best advice: “Do no harm!” For idiopathic cases (erythema multiforme, cutaneous vasculitis, miliary dermatitis), consider hydrolysate treated or home-cooked elimination diet trial.

**Supportive Therapy—IV Fluids**

Systemic antibiotics in septic patients, broad spectrum initially and based on results of culture and susceptibility. Cephalexin—10 mg/lb TID, but if Gram negative organisms are present use Ciprofloxacin—22 mg/kg SID.
Immunosuppressive Drugs

Extremely controversial and may actually be contraindicated due to increased risk of infections and delayed healing. Are specifically indicated in drug-induced erythema multiforme major.

Corticosteroids: Prednisolone—1 mg/lb SID-BID.

Immune modulating drugs: Cyclophosphamide—1 mg/lb SID, Cyclosporine (Neoral, Gengraf, Atopica)—5 mg/kg SID-BID. Azathioprine (Imuran)—1 mg/lb SID, Pentoxifylline (Trental)—15 mg/kg TID.