12
DERMATOLOGY

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Eczema

DIFFERENTIAL DIAGNOSIS OF PRURITUS

INFLAMMATORY

- **DERMATITIS**—atopic dermatitis, asteatotic eczema, nummular eczema, dyshidrotic eczema, seborrheic dermatitis, stasis dermatitis, irritant contact dermatitis, allergic contact dermatitis, lichen simplex chronicus (neurodermatitis)
- **PSORIASIS**
- **PITYRIASIS LICHENOIDES**
- **URTICARIA**
- **DERMATITIS HERPETIFORMIS**
- **BULLOUS PEMPHIGOID**
- **LINEAR IMMUNOGLOBIN A DISEASE**
- **GRAFT VS HOST DISEASE**

INFECTIONS—tinea, scabies, pediculosis corporis and pubis, pityriasis rosea, varicella

NEOPLASTIC—lymphoma (mycosis fungoides, Hodgkin lymphoma), myeloma, solid tumors, polycythemia vera

IATROGENIC

- **DRUG ERUPTION**—antibiotics, anti-epileptics
- **DRUG-INDUCED PRURITUS**—opiates, steroids, aspirin, antimalarials

SYSTEMIC

- **ENDOCRINE**—diabetes, hypothyroidism, hyperthyroidism, carcinoid syndrome
- **HEPATOBILIARY**—PBC, cholestasis
- **RENAL**—uremia, hemodialysis
- **NEUROLOGIC**—brachioradial pruritus, notalgia paresthetica, postherpetic neuralgia, multiple sclerosis
- **INFECTIONS**—HCV, HIV
- **AUTOIMMUNE**—sarcoidosis, dermatomyositis, Sjögren syndrome
- **PSYCHOGENIC**—delusional infestation, psychogenic excoriation, anorexia nervosa
- **OTHERS**—iron deficiency, idiopathic xerosis, burns and scars

PATHOPHYSIOLOGY

PATHOGENESIS—chronic inflammatory skin disorder characterized by dry skin and pruritus. Rubbing and scratching the skin promotes inflammation and leads to an itch–scratch cycle. It follows a relapsing course characterized by alternating periods of flares and remissions. Mutations in filaggrin and deficiency in ceramides play a key role in pathogenesis. Patients often have a personal or family history of eczema, asthma, or allergic rhinitis. Exacerbating factors may include cold weather, dust mites, pollens, infection, wool, pet fur, emotional stress, chemical irritants, and other allergens

CLINICAL FEATURES

FINDINGS—ill-defined pruritic erythematous plaques with excoriations. Neck and flexural prominence in adults and children. Extensor prominence in infants. Pustules, honey-colored crusts, and weeping may be a sign of secondary infection

TYPES OF ECZEMA

- **ASTEATOTIC ECZEMA**—dry irritable skin in the elderly
- **NUMMULAR ECZEMA**—acral, coin-shaped patches of eczema usually on extremities
- **DYSHIDROTIC ECZEMA**—acute vesicular eczema of the palms and soles
- **XEROSIS/WINTER ITCH**—eczema secondary to dry conditions in winter

INVESTIGATIONS

SPECIAL (not typically performed)

- **LABS**—CBC (eosinophilia) and IgE level (elevated)
- **BACTERIAL AND VIRAL CULTURES**—if there is a suspicion of a secondary infection

D. Hui et al. (eds.), *Approach to Internal Medicine*,
https://doi.org/10.1007/978-3-030-72980-6_12

MANAGEMENT

TREATMENTS—**dry skin care** (unscented, hypoallergenic soaps, daily moisturizers). **Topical corticosteroids** BID × 3 weeks, off 1 week, repeat PRN (typically hydrocortisone 1–2.5% or desonide 0.05% for the face, triamcinolone 0.1% for the body), and topical calcineurin inhibitors (tacrolimus 0.1%, pimecrolimus 1%). **Antihistamines** (diphenhydramine, loratadine, fexofenadine, hydroxyzine, and doxepin). **Oral antibiotics** × 7 days for superimposed *Staphylococcus aureus* infections (typically flucloxacillin or other penicillinase-resistant penicillin for MSSA and clindamycin, doxycycline or trimethoprim-sulfamethoxazole for MRSA)

SPECIFIC ENTITIES

DERMATITIS HERPETIFORMIS

- **ASSOCIATIONS**—celiac disease, IgA nephropathy, autoimmune thyroid disease, autoimmune hepatitis, type 1 diabetes, SLE, Sjögren syndrome, sarcoidosis, Addison disease, atrophic gastritis, vitiligo, and alopecia areata. Strong linkage to HLA-B8, DR3, and DQw2. Increased risk of non-Hodgkin lymphoma
- **CLINICAL FEATURES**—pruritic erythematous papulovesicles on extensor surfaces and buttocks, rarely mucous membranes. Lesions tend to be symmetrically distributed
- **TREATMENTS**—dapsone and gluten-free diet. If dapsone cannot be tolerated, sulfonamides such as sulfasalazine can be used. See Celiac Disease (p. 142)

STASIS DERMATITIS

- **CLINICAL FEATURES**—erythematous pruritic and burning lesions found on lower limbs of older patients due to compromised venous or lymphatic return. With increased extravasation of blood into the surrounding tissues, the lesions become darker, scalier, and may even form stasis ulcers and lipodermatosclerosis in late disease. Accompanying localized hair loss may be seen
- **TREATMENTS**—treat underlying cause. Encourage weight reduction, daily walking/exercise, and leg elevation as tolerated. Graduated compression stockings (after ankle–brachial index [ABI] checked). Topical steroids for acute exacerbations. Pharmacologic systemic therapy, such as venoactive or phlebotonic drugs, pentoxifylline, and flavonoids have been used. Varicose veins may be treated with surgery, endovenous laser therapy or via sclerotherapy

SCABIES

- **CLINICAL FEATURES**—excoriations, eczematized and urticarial papules over trunk. Linear white burrows over finger webs, sides of hand, and flexural aspects of wrists. Confirmed by skin scrapings for ectoparasitic mites and eggs. Crusted scabies is a severe form seen in HIV and immunosuppressed patients
- **TREATMENTS**—first-line therapy with *permethrin* 5% cream × 1 dose, applied to the entire body from chin to soles, rinse off after 8–14 h. Second-line treatments include *ivermectin* 200 mcg/kg PO × 1 dose and repeat PO × 1 dose 1–2 weeks later, *lindane* 1% lotion or cream × 1 dose, rinse off after 8 h, and *benzyl benzoate* 10 or 25% lotions × 1 dose, rinse off after 24 h. Simultaneous treatment of patient and close contacts is recommended

Chosidow *NEJM* 2006;354(16)
Thomas et al. *J Am Acad Dermatol* 2020;82(3)

Psoriasis Vulgaris

DIFFERENTIAL DIAGNOSIS OF PAPULOSQUAMOUS LESIONS

INFLAMMATORY—psoriasis vulgaris, lichen planus, nummular eczema, discoid lupus
INFECTIONS—tinea, pityriasis rosea, secondary syphilis, seborrheic dermatitis
MALIGNANCY—mycosis fungoides, basal cell carcinoma (BCC), squamous cell carcinoma (SCC)
IATROGENIC—drug eruption

PATHOPHYSIOLOGY

INFLAMMATION—a chronic inflammatory skin disorder with a polygenic predisposition and sometimes an environmental triggering factor (trauma/Koebner phenomenon, infections, drugs, smoking, alcohol ingestion, emotional stress)

CLINICAL FEATURES

FINDINGS—well-circumscribed, bright salmon red color, silvery micaceous scaly plaques. Predilection for the scalp and extensor regions. Nails may show pitting changes, "oil spots", onycholysis, and subungual debris that may be helpful in making the diagnosis. All patients regardless of skin severity should be screened for inflammatory arthritis that is worse in the mornings, associated with joint stiffness and swelling ± dactylitis. Consider screening for hyperlipidemia, coronary artery disease, and diabetes in patients with risk factors as there is an increased predilection in patients with psoriasis

SUBTYPES

- **CHRONIC PLAQUE PSORIASIS**—predilection for scalp, elbows, and knees. Symmetric, sharply demarcated erythematous plaques with silvery scales that when scratched off reveal punctate blood droplets (Auspitz sign)
- **GUTTATE PSORIASIS**—predilection for trunk. May follow a streptococcal infection. Multiple discrete erythematous papules with silvery scales
- **PALMOPLANTAR PSORIASIS**—mild to severe forms. Well-demarcated erythematous plaque with silver scales. Cracking, fissures, or bleeding may be seen. Pustular variant also found
- **INVERSE PSORIASIS**—perianal, genital, and axillary well-demarcated erythematous plaques that are more likely to be macerated and fissured due to location in a moist and warm environment
- **ERYTHRODERMIC PSORIASIS**—generalized erythema ± characteristic erythematous plaques with white-silver scale and nail changes. Often spares the face
- **PUSTULAR PSORIASIS**—initial stinging and burning in area may promote scratching, followed by eruption of sterile pustules. Hypocalcemia is a risk factor
- **NAIL PSORIASIS**—multiple small nail pits, leukonychia, red macules on nail lunula, and degradation of the nail plate. Associated with psoriatic arthritis

INVESTIGATIONS

SPECIAL (not typically performed)

- **MICROBIOLOGY**—throat C&S (if guttate psoriasis)
- **KOH PREPARATION**—if suspect tinea
- **SKIN BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE—**topical therapy** with corticosteroids (triamcinolone/fluocinolone, fluocinonide, betamethasone dipropionate and clobetasol), emollients, and vitamin D analogs. **Topical calcineurin inhibitors** may be used on the face and intertriginous areas. If unable to control, **light therapy** with either UVB or PUVA may be considered but requires 2–3 visits/week for months. Traditional **systemic therapies** including acitretin, cyclosporine, apremilast, and methotrexate should be considered in patients with moderate to severe psoriasis with >10% body surface involvement or severe functional impairment (hands, feet, arthritis, and genitals). If unresponsive or unable to tolerate these, **biologic therapy** such as the **TNFα inhibitors** (infliximab, adalimumab, golimumab, etanercept), **IL-17 pathway inhibitors** (secukinumab, ixekizumab, brodalumab), or **IL-23 pathway inhibitors** (ustekinumab, guselkumab, tildrakizumab) should be considered for psoriatic arthritis. Avoid systemic steroids as discontinuation may cause generalized pustular psoriasis

SPECIFIC ENTITIES

PITYRIASIS ROSEA

- **PATHOPHYSIOLOGY**—human herpesvirus-6/7 may be the etiologic agent, although this disorder does not seem to be contagious
- **CLINICAL FEATURES**—herald plaque (2–5 cm, round, redder, scaly) followed by many smaller oval plaques in a "Christmas tree" configuration involving the trunk and extremities. Resolves spontaneously after 2–5 weeks
- **TREATMENTS**—no treatment needed usually. Topical steroid to relieve pruritus

LICHEN PLANUS

- **PATHOPHYSIOLOGY**—autoimmune disease with lymphocytic infiltration in epidermis
- **ASSOCIATIONS**—drugs (β-blockers, methyldopa, penicillamine, NSAIDs, ACE inhibitors, carbamazepine, gold, lithium), HCV infection
- **CLINICAL FEATURES ★5 P's★**—**P**urple, **P**ruritic, **P**olygonal, **P**lanar (flat-topped) **P**apules. May also see fine white lines on the surface (Wickham striae). Commonly seen in flexor wrists, forearms, and buccal mucosal (lacy white reticular lesions). Lesions may last for a year

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—no treatment needed usually. Topical or intralesional steroids, antihistamines, and anti-inflammatories to relieve pruritus. Investigate for associated causes

SEBORRHEIC DERMATITIS

- **PATHOPHYSIOLOGY**—a common skin disorder affecting areas rich in sebaceous glands such as the scalp, face, mid-chest, and intertriginous areas. It is caused by the yeast *Malassezia furfur* (formerly known as *Pityrosporum ovale*), *M. restricta*, and *M. globosa,* with increased host response leading to dermatitis. It is also known as "dandruff" in adults. Severe seborrheic dermatitis is associated with stress, neurologic disease (e.g. Parkinson disease), and immunosuppression (e.g. HIV/AIDS)
- **CLINICAL FEATURES**—pink to erythematous plaques with yellow scales or greasy crusts, which may occasionally be pruritic
- **TREATMENTS**—gentle emollients, ketoconazole shampoo or cream, 1–2.5% hydrocortisone cream, or topical calcineurin inhibitors. Severe scalp involvement in an adult may also be treated with shampoos containing selenium sulfide, zinc pyrithione, and stronger steroid liquids

Related Topic
Psoriatic Arthritis (p. 302)

URTICARIA (HIVES)

- **PATHOPHYSIOLOGY**—an acute (<6 weeks) or chronic (>6 weeks) type I hypersensitivity reaction. Most cases are idiopathic but triggers may include infections, insect bites, certain foods, medications, and emotional stress
- **CLINICAL FEATURES**—characterized by superficial transient edema with pink highly pruritic papules or plaques (wheals) with individual lesions having rapid onset and resolution within 24 h. Dermatographism is common where wheals may be induced after stroking the skin
- **TREATMENTS**—identification and elimination of eliciting factors, non-sedating antihistamines during the day and scheduled sedating antihistamines at night. Systemic glucocorticoids may be used when severe, but courses should be tapered over 5–7 days

SPECIFIC ENTITIES (CONT'D)

DERMATOPHYTE (TINEA) INFECTIONS

- **PATHOPHYSIOLOGY**—*Trichophyton*, *Epidermophyton*, *Microsporum* are fungi that can uniquely dissolve keratin
- **CLINICAL FEATURES**—asymptomatic, scaling erythematous patches/plaques that slowly enlarge over scalp (tinea capitis), feet (tinea pedis), hand (tinea manuum), groin (tinea cruris), body (tinea corporis), and nails (onychomycosis). May be associated with pruritus and vesicles
- **DIAGNOSIS**—skin and nail lesions may be difficult to distinguish from psoriasis, eczematous conditions, and lichen planus. KOH examination from skin scrapings shows segmented hyphae and spores
- **TREATMENTS**—**tinea capitis** (*griseofulvin* 20–25 mg/kg/day for 6–8 weeks, terbinafine, itraconazole), **tinea pedis or cruris** (*terbinafine* 1% cream daily-BID, *clotrimazole/Lotrimin*® 1% cream BID), **onychomycosis** (*terbinafine* 250 mg PO daily × 6–12 weeks, *itraconazole* 200 mg PO daily × 8–12 weeks. Need to monitor liver enzymes)

TINEA VERSICOLOR

- **PATHOPHYSIOLOGY**—*Malassezia furfur*
- **CLINICAL FEATURES**—young adult with hypopigmented, light brown, or salmon-colored scaly macules coalescing into patches
- **DIAGNOSIS**—KOH examination from skin scrapings show classic "spaghetti and meatballs" pattern representing hyphae and spores
- **TREATMENTS**—**topical** (*terbinafine* 1% cream daily BID, *clotrimazole* 1% cream BID, selenium sulfide 2.5% shampoo or lotion), **systemic** (ketoconazole, fluconazole, itraconazole)

GROIN SKIN LESIONS—common causes include tinea cruris, candidiasis, erythrasma (*Corynebacterium minutissimum*), and inverse psoriasis

Acne Vulgaris

James *NEJM* 2005;352(14)
Zaenglein *NEJM* 2018;379(14)

DIFFERENTIAL DIAGNOSIS OF ACNEIFORM LESIONS

ACNE VULGARIS
ROSACEA
PERIORIFICIAL DERMATITIS
DRUGS—**EGFR inhibitors** (erlotinib, gefitinib, cetuximab, panitumumab) and **oral corticosteroids** (prednisone, dexamethasone) can cause pustular folliculitis
PSEUDOFOLLICULITIS BARBAE
FACIAL ANGIOFIBROMAS—tuberous sclerosis, multiple endocrine neoplasia type 1, Birt-Hogg-Dubé syndrome

PATHOPHYSIOLOGY

PATHOGENESIS—condition affecting pilosebaceous units, commonly seen during puberty. Pathogenesis involves androgens, follicular keratinization, and the Gram-positive bacteria *Propionibacterium acnes*. Lesions may present as non-inflammatory comedones or inflammatory papules. Inflammatory cysts may leave behind hyperpigmentation and sometimes scarring
RISK FACTORS—**drugs** (steroids, phenytoin, lithium), **androgen excess** (PCOS, Cushing disease, congenital adrenal hyperplasia), skin trauma, family history. Diet, stress, insulin resistance, and body mass index may contribute to lesion development

CLINICAL FEATURES

SEVERITY OF ACNE VULGARIS

- **MILD**—mainly comedones with few papules/pustules
- **MODERATE**—moderate papules and pustules (10–40) and comedones (10–40)
- **MODERATELY SEVERE**—numerous papules and pustules (40–100) and many comedones (40–100). May have nodular inflamed lesions (up to 5). Widespread involvement of face, chest and back
- **SEVERE**—nodulocystic acne and acne conglobata with many nodular or pustular lesions

TYPICAL PRESENTATION—teenager with open comedones (blackheads), closed comedones (whiteheads), erythematous papules, pustules, cysts and scarring over face, shoulders, upper chest, and back

INVESTIGATIONS

SPECIAL (not typically performed)

- **ENDOCRINE WORKUP**—testosterone, 24-h urinary cortisol

MANAGEMENT

TREAT UNDERLYING CAUSE

- **MILD CASES**—topical agents include benzoyl peroxide 2.5–10% daily-BID, sulfur-based washes, topical retinoids (*tretinoin* 0.025–0.1% qhs, *tazarotene* qhs), and topical antibiotics (*clindamycin* daily-BID, *erythromycin* daily-BID)
- **MODERATE CASES**—in addition to above agents for mild cases, oral antibiotic (*minocycline* 50–100 mg daily-BID, *doxycycline* 50–100 mg daily-BID, *trimethoprim–sulfamethoxazole* 160/800 BID, *tetracycline* 250–500 mg daily-BID, *erythromycin* 250–500 mg BID–QID) or antiandrogen therapy such as birth control pills may be used in female patients
- **SEVERE CASES**—respond well to oral *isotretinoin* 0.5–1 mg/kg/day, with a cumulative dose of 120 mg/day. Close monitoring with laboratory and clinical follow-up. High risk for teratogenicity

TREATMENT ISSUES

RETINOIDS—inhibit sebum excretion and *P. acnes*. Reserved for severe nodulocystic acne. Topical retinoids may cause irritation and dryness of the skin. Retinoids should never be used in pregnant women as highly teratogenic. Fertile women should take oral contraceptive pills 2 months before treatment continuing until 1 month after discontinuing oral retinoids

SPECIFIC ENTITIES

ROSACEA

- **CLINICAL FEATURES**—middle age adults with central facial telangiectasias, flushing (especially after ingestion of hot liquids, alcohol, spicy foods, heat, and other triggers), and acneiform papulopustules on cheeks, nose, forehead, and chin. No comedones. May be associated with rhinophyma (more in men), conjunctivitis, iritis, and keratitis
- **TREATMENTS**—oral antibiotics (tetracycline, erythromycin), topical antibiotics (metronida-

SPECIFIC ENTITIES (CONT'D)

zole 0.75%), sulfur-based products (sodium sulfacetamide lotion 10%), pulsed dye laser. Advanced phymatous skin changes can be treated with laser ablation. Avoidance of flushing triggers and daily sun protection are advised

PERIORAL (PERIORIFICIAL) DERMATITIS

- **CLINICAL FEATURES**—young woman with papules and pustules over chin, upper lip, and nasal labial folds

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—topical therapeutic options include *pimecrolimus* 1% cream or *erythromycin* 2% gel applied twice daily. *Metronidazole* 1% lotion or gel can be applied once daily. Oral tetracyclines may be used for moderate to severe disease. Discontinuation of topical corticosteroids and other topical irritants if relevant

Exanthematous Lesions

DIFFERENTIAL DIAGNOSIS OF EXANTHEMATOUS LESIONS

INFECTIONS

- **VIRAL**—HCV, HIV, EBV, parvovirus B19, measles, rubella, roseola
- **BACTERIAL**—toxic shock, staphylococcal scalded skin syndrome, streptococcal toxic shock syndrome, scarlet fever, meningococcus, Rocky Mountain spotted fever, typhus

IATROGENIC—medications (see DRUG ERUPTIONS p. 412)

CLINICAL FEATURES

TYPICAL PRESENTATION—widespread erythematous maculopapular lesions that may be accompanied by fever and malaise

MANAGEMENT

TREAT UNDERLYING CAUSE—discontinue any offending drugs. Usually resolve spontaneously

Related Topic
Fever and Rash (p. 248)

SPECIFIC ENTITIES

PARVOVIRUS B19—slapped cheek rash on face and erythematous eruption on trunk, neck, and extremities, which is most common in children. Also called fifth disease or erythema infectiosum. Self-limiting. Fever may be present. Parvovirus B19 is also associated with aplastic anemia, polyarthritis, and fetal hydrops

SPECIFIC ENTITIES (CONT'D)

STAPHYLOCOCCAL SCALDED SKIN SYNDROME (SSSS)

- **PATHOPHYSIOLOGY**—exfoliatins produced by specific strains of staphylococci leading to desquamative disorder with cleavage at the granular layer of the dermis and acute epidermolysis. Most common in infants
- **CLINICAL FEATURES**—fever, malaise, generalized macular erythematous rash that evolves rapidly into a scarlatiniform (sandpaper-like) rash, followed by an exfoliative phase with perioral exudation and crusting. Large radial fissures "sunburst" around the mouth and are one of the diagnostic features. Nikolsky sign positive. Increased risk in children/infants, renal failure, immunocompromised
- **DIAGNOSIS**—culture from a site other than the blisters (blood, conjunctivae, nasopharynx) demonstrating staphylococci
- **TREATMENTS**—hospitalization for supportive care, culture for antibiotic susceptibility, and IV antibiotics for treatment of staphylococci (nafcillin/oxacillin first line, vancomycin if failing therapy or high prevalence or risk of MRSA)

SCARLET FEVER

- **PATHOPHYSIOLOGY**—erythrogenic toxin by specific strains of group A *Streptococcus* leading to cleavage at the granular layer of the dermis
- **CLINICAL FEATURES**—children with fever, sore throat, petechiae, and punctate red macules on hard and soft palate and uvula (Forchheimer spots), circumoral pallor, strawberry tongue, erythematous patches involving ears and chest, extend to trunk and extremities and accentuate in skin folds (Pastia lines). Evolves

SPECIFIC ENTITIES (CONT'D)

to sandpaper-like appearance. Desquamation occurs 7–10 days after resolution of rash

- **TREATMENTS**—antibiotics to treat scarlet fever symptoms, prevent contagious spread of group A *Streptococcus*, and to prevent acute rheumatic fever. Penicillin V is first-line. Fluid resuscitation as needed

Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis

DIFFERENTIAL DIAGNOSIS OF VESICLES/BULLOUS LESIONS

INFLAMMATORY—bullous pemphigoid*, pemphigus vulgaris*, porphyria cutanea tarda*, lupus*, dermatitis herpetiformis, erythema multiforme, contact dermatitis, linear IgA bullous dermatosis, epidermolysis bullosa acquisita, pemphigoid gestationis

INFECTIONS

- **BACTERIAL**—bullous impetigo*, staphylococcal scalded skin syndrome, toxic shock syndrome
- **VIRAL**—HSV, VZV, molluscum contagiosum, Coxsackie virus

NEOPLASTIC—paraneoplastic pemphigus

IATROGENIC—Stevens–Johnson syndrome*, toxic epidermal necrolysis*

*bullous lesions may be seen with or without vesicles

PATHOPHYSIOLOGY

HYPERSENSITIVITY REACTION—Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) lie on a spectrum of serious, life-threatening illness characterized by extensive epidermal necrosis. By definition, SJS involves less than 10% of the body surface area (BSA) and TEN involves greater than 30% of the BSA. Involvement of 10–30% BSA is an overlap between the two. Drugs are the most common offending agents, but *Mycoplasma pneumoniae*, viruses, various chemicals and immunizations have also been associated with SJS/TEN

COMMONLY ASSOCIATED DRUGS ★4A'S★

- **ALLOPURINOL**
- **ANTIBIOTICS**—sulfamethoxazole, cephalosporins, penicillins, quinolones, macrolides
- **ANTI-INFLAMMATORY DRUGS**—NSAIDs, salicylates
- **ANTICONVULSANTS**—carbamazepine, phenytoin, lamotrigine, phenobarbital

RISK FACTORS—HIV infection, malignancy (particularly hematologic cancers), certain HLA types, SLE, high doses of the drugs listed above

CLINICAL FEATURES

TYPICAL PRESENTATION—patients usually develop symptoms within 2–3 weeks after drug exposure, more rapidly in previously exposed patients. The prodrome involves a flu-like syndrome with fever, malaise, arthralgias, myalgias, and mucous membrane lesions. This is followed by the development of irregular target-like lesions often with necrotic centers that coalesce over time. Flaccid blisters form that spread with pressure (Nikolsky sign), resulting in sheet-like loss of epidermis and exposure of the underlying dermis. Ninety percent of patients have mucous membrane involvement, 60% have ocular involvement, and up to two-thirds of patients may develop urethritis or have other urogenital involvement

NIKOLSKY SIGN—pressing on the edges of an intact blister helps to discriminate between an intraepidermal blistering process (pemphigoid vulgaris, blister extends and breaks easily) and a subepidermal process (TEN, bullous pemphigoid, blister would not advance)

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, Cr, urea
- **MICROBIOLOGY**—fluid C&S, HSV serology, VZV serology
- **SKIN BIOPSY**

PROGNOSTIC ISSUES

PROGNOSIS—mortality rates for SJS and TEN are approximately 5% and 30–50%, respectively, typically from sepsis and multi-organ failure. The risk of death can be predicted using the TEN specific severity-of-illness score (SCORTEN). Prognostic factors are each assigned a score of 1 and then added together to determine the predicted mortality

PROGNOSTIC ISSUES (CONT'D)

Prognostic factor	Weight	SCORTEN total	Predicted mortality
Age ≥40	1	0-1	3.2%
Heart rate ≥120/min	1	2	12.1%
Associated malignancy	1	3	35.8%
Initial BSA skin detachment >10%	1	4	58.3%
Serum urea >10 mmol/L [27 mg/dL]	1	5 or more	90%
Serum glucose >14 mmol/L [252 mg/dL]	1		
Bicarbonate >20 mmol/L [20 mEq/L]	1		

Bastuji-Garin et al. *J Invest Dermatol* 2000;115(2)

MANAGEMENT

TREAT UNDERLYING CAUSE—identifying and **stopping the offending drug**. **Corticosteroids** may be helpful but can be deleterious in severe forms of SJS/TEN. **High-dose IVIG** is controversial but may halt progression. Corticosteroids and IVIG in combination therapy may reduce mortality in TEN and SJS/TEN overlap. Systemic antibiotics may be necessary, but prophylactic systemic antibiotics are not empirically used. Infection control is employed with sterile handling, antiseptic solutions (although silver sulfadiazine should not be used if sulfonamides are thought to be the cause of SJS/TEN), and repeated skin, blood and catheter cultures every 48 hours. Promising newer treatments include cyclosporine and etanercept

SUPPORTIVE MEASURES—patients should be managed in a burn unit or ICU, as electrolyte abnormalities, renal failure, and pulmonary edema may occur. Pain control, wound and ocular care, adequate fluid replacement, prevention of infection and vulvovaginal complications, nasogastric tube feeding, heated room temperature to 30°C to 32°C

Seminario-Vidal et al. *J Amer Acad Dermatol* 2020;82(6)

SPECIFIC ENTITIES

ERYTHEMA MULTIFORME

- PATHOPHYSIOLOGY—immune-mediated hypersensitivity reaction involving the skin and potentially mucous membranes (very limited)
- ASSOCIATIONS—infections (HSV, HBV, HCV, *Mycoplasma*, bacterial, fungal), drugs, pregnancy, malignancy
- CLINICAL FEATURES—skin lesions usually preceded by a few weeks of viral prodrome. Macules or papules evolve to form targetoid lesions. Palms, soles, forearms, legs most commonly affected
- TREATMENTS—discontinue offending drugs. Treat suspected HSV infection with appropriate antivirals. Topical corticosteroids or oral antihistamines are appropriate symptomatic therapies, and intra-oral lesions may be palliated with an anesthetic mouthwash. Patients with significant ocular involvement should be referred to an ophthalmologist. Patients who fail systemic antiviral therapy may be treated with mycophenolate, dapsone, mofetil, azathioprine, or cyclosporine. Tofacitinib and apremilast are newer treatment options for refractory cases

BULLOUS IMPETIGO

- PATHOPHYSIOLOGY—intra-epidermal infection by *S. aureus* or β-hemolytic streptococci
- CLINICAL FEATURES—in bullous form, flaccid, pus-filled lesions often found in intertriginous areas and on the trunk, which rupture to form a golden-brown crust. More commonly found in children. Management of bullous impetigo in an adult should include a work-up for HIV infection
- TREATMENTS—limited impetigo can be treated with topical therapy (mupirocin TID or retapamulin BID × 5 days); however extensive impetigo warrants systemic antibiotics (cephalexin, dicloxacillin, and clindamycin)

BULLOUS PEMPHIGOID

- PATHOPHYSIOLOGY—autoimmune blistering disease with IgG binding to subepidermal proteins (BP antigen 180 or 230), leading to separation of epidermis from dermis
- ASSOCIATIONS—furosemide, captopril, thiazide, spironolactone, penicillamine, phenothiazines, tricyclic antidepressants, benzodiazepines

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—multiple chronic, pruritic, tense blisters in the elderly. Commonly affecting flexural areas, axillae, and groin. Mucous membranes affected in <1/3 of cases, but rarely presenting feature. Nikolsky sign negative
- **TREATMENTS**—discontinue offending drugs. In mild or localized disease, treat with Class I topical steroids (clobetasol propionate 0.05% cream). Treat with anti-inflammatories and immunosuppressants, including tetracycline in conjunction with niacinamide. *Prednisone* 1–2 mg/kg PO daily. Methotrexate, azathioprine and mycophenolate mofetil are glucocorticoid-sparing options

PEMPHIGUS VULGARIS

- **PATHOPHYSIOLOGY**—autoimmune blistering disease with IgG binding to intraepidermal proteins (desmoglein 1 and 3), leading to separation of keratinocytes in epidermis
- **ASSOCIATIONS**—penicillamine, captopril, enalapril, penicillins, cephalosporins, malignancies (paraneoplastic)
- **CLINICAL FEATURES**—acute onset of multiple flaccid blisters. Mucous membranes usually affected first, with spread to scalp, face, chest, and groin. Nikolsky sign positive. Lesions prone to rupture and infections. May be life-threatening. May be paraneoplastic
- **TREATMENTS**—discontinue offending drugs. Consider burn unit admission, supportive fluids. *Prednisone* 1–2 mg/kg PO daily. Azathioprine, cyclosporine, mycophenolate mofetil, rituximab, plasmapheresis, IVIG

HERPES SIMPLEX VIRUS (HSV) 1 OR 2

- **CLINICAL FEATURES**—vesicles followed by ulcers in oral (gingivostomatitis) or genital areas
- **DIAGNOSIS**—scraping of vesicle stained with Wright–Giemsa stain shows acantholytic ballooned and multi-nucleated cells. Viral culture, PCR, direct fluorescent antibody, and serologic antibody testing are other diagnostic tools
- **TREATMENTS**—acyclovir, valacyclovir, famciclovir

VARICELLA ZOSTER VIRUS (VZV)

- **CLINICAL FEATURES**—crops of vesicles over entire body (varicella) or specific dermatome with reactivation (zoster, also known as shingles)
- **TREATMENTS**—acyclovir, valacyclovir, famciclovir. Amitriptyline, gabapentin, and opioids may be useful for post-herpetic neuralgia
- **PREVENTION**—vaccination in immunocompetent patients at least 50 years old is recommended, even in patients with prior herpes zoster infections (however, must delay vaccination for 1 year after infection). The two types of zoster vaccines are the recombinant zoster vaccine (RZV) (Shingrix®) and the live attenuated vaccine (ZVL) (Zostavax®). RZV is the recommended choice for most patients because the evidence suggests it has greater efficacy over a longer period of time. However, ZVL requires one dose, while RZV is a two-part series, and ZVL has a lower incidence of systemic side effects than RZV

Ulcers

DIFFERENTIAL DIAGNOSIS OF ULCERS

VENOUS HYPERTENSION

- **STASIS**—immobility, CHF, incompetent valves, pregnancy
- **DVT**

ATHEROSCLEROTIC—ischemic ulcers, hypertensive ulcers (Martorell hypertensive ulcer)

NEUROPATHIC—diabetes, leprosy, syphilis, syringomyelia, peripheral neuropathy

VASCULITIC—temporal arteritis, polyarteritis nodosa, systemic sclerosis

INFECTIONS

- **BACTERIAL**—gumma, mycobacteria
- **VIRAL**—chronic ulcerative herpes simplex
- **FUNGAL**—deep fungal infections
- **PARASITIC**—cutaneous leishmaniasis, cutaneous amebiasis

DIFFERENTIAL DIAGNOSIS OF ULCERS (CONT'D)

TUMOR—squamous cell carcinoma, basal cell carcinoma, melanoma, Kaposi sarcoma

TRAUMA—pressure-induced skin injury, burns

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, glucose, urea, Cr, HbA1C
- **MICROBIOLOGY**—wound Gram stain, AFB, C&S, TB culture
- **ANKLE BRACHIAL INDEX**—<0.8 indicates arterial origin
- **IMAGING**—doppler US, venous plethysmography

INVESTIGATIONS (CONT'D)

SPECIAL (workup for pyoderma gangrenosum specifically)

- **COLONOSCOPY**—if suspect IBD
- **MALIGNANCY WORKUP**—serum protein electrophoresis, CXR
- **INFLAMMATORY WORKUP**—ESR, antiphospholipid antibody, antineutrophil cytoplasmic antibodies, cryoglobulins
- **SKIN BIOPSY**—mainly to rule out possible skin malignancies in the ulcer and to exclude other diagnoses. Include inflamed border for histologic evaluation and ulcer edge for bacterial, fungal, and mycobacterial culture

MANAGEMENT

See SPECIFIC ENTITIES for details

SPECIFIC ENTITIES

VENOUS ULCERS

- **PATHOPHYSIOLOGY**—result from chronic increases in venous pressure due to either incompetent valves, failure of pump activity from immobility or obesity, or venous outflow obstruction. Increased pressure in the venous system results in dilatation of the capillary beds and chronic inflammation that breaks down the extracellular matrix
- **RISK FACTORS**—obesity, HF, history of DVT and/or thrombophlebitis, varicose veins, prolonged standing, and multiple pregnancies
- **CLINICAL FEATURES**—shallow, irregular borders, relatively painless, and typically located from the mid-calf to the ankle, classically on the medial malleolus. Other common lower extremity findings include edema, lipodermatosclerosis (firm and indurated skin), hyperpigmentation, and dermatitis
- **TREATMENTS**—compression stockings (need to rule out arterial insufficiency), leg elevation, walking/physiotherapy. Occlusive dressing (DuoDerm® weekly if not infected vs. twice daily if infected). Diuretics (decrease leg edema). Antibiotics if super-infected. Superficial vein surgery may prevent recurrence in some patients

ATHEROSCLEROTIC ULCERS

- **PATHOPHYSIOLOGY**—result from peripheral artery disease or vasculitis that prevents adequate blood flow to the lower extremity. Inadequate oxygen and nutrient delivery results in tissue breakdown and arterial necrosis
- **RISK FACTORS**—atherosclerosis, peripheral artery disease, diabetes mellitus, obesity, smoking, rheumatic disease, Buerger disease, hemoglobinopathies
- **CLINICAL FEATURES**—ulcers tend to be well defined and appear "punched out" with a gray or black necrotic base. Lesions occur over distal sites such as toes and bony prominences and are very painful. Associated features include intermittent claudication, diminished peripheral pulses, and prolonged capillary refill (greater than 3 to 4 seconds)
- **TREATMENTS**—treat underlying cause, such as surgical bypass for peripheral arterial disease. Avoidance of trauma. Apply moist occlusive dressings. Surgical debridement and systemic antibiotics may be necessary if infected. See PERIPHERAL VASCULAR DISEASE (p. 67)

NEUROPATHIC ULCERS

- **PATHOPHYSIOLOGY**—most common in diabetic patients. A combination of sensory and motor neuropathy due to enzymatic glycosylation impairs protective sensation and alters the distribution of forces on the lower extremity during normal movement. Many diabetic patients have a combination of neuropathic and arterial ulcers
- **RISK FACTORS**—diabetes mellitus, syphilis, leprosy, and peripheral neuropathies
- **CLINICAL FEATURES**—a pure neuropathic ulcer is painless. There is diminished sensation in the lower extremity. Patients have warm extremities with palpable pulses, as opposed to arterial ulcers
- **TREATMENTS**—diabetic patients require tight glucose control. Treat infection with systemic antibiotics. Debridement of the ulcer, hyperbaric oxygen therapy, and occlusive dressings are applied to promote wound healing. Immobilization and orthotic devices are used to alleviate pressure on the wound. Amputation may be required in severe cases

PYODERMA GANGRENOSUM

- **PATHOPHYSIOLOGY**—chronic condition that involves neutrophilic destruction of tissue
- **RISK FACTORS**—approximately 50% of patients have an underlying systemic illness, including ulcerative colitis (most common), Crohn disease, rheumatoid arthritis, lymphoproliferative disorder (lymphoma, leukemia, MDS), Behçet disease, and active hepatitis
- **CLINICAL FEATURES**—initially lesions appear as small, painful, erythematous papules that spread concentrically, evolving into pustules. Tissue breakdown and ulceration occur rapidly. Ulcers classically have dusky-red, violaceous,

SPECIFIC ENTITIES (CONT'D)

irregular borders with a purulent exudate and undermining. Lesions are typically solitary but may be multiple and coalesce into larger ulcers. It is typically found on the lower extremity, but other common sites include the buttocks, abdomen, and face. Exhibits pathergy, often arising in sites of injury (surgical incision, needle prick, insect bite). ESR may be elevated. Classically worsens with attempted biopsy or debridement

- **TREATMENTS**—treat underlying causes where possible and maintain a moist wound environment to facilitate healing. Immunosuppressive and immunomodulator therapy with systemic corticosteroids (*prednisone* 60–80 mg PO daily, *pulse methylprednisolone* 1 g IV daily×3 days), cyclosporine, and biologics such as infliximab and canakinumab have the greatest evidence for treatment. Adjunct treatment with intralesional steroids injected at active border sites and topical calcineurin inhibitors (tacrolimus) may improve outcomes. Other options include IVIG, sulfasalazine, sulfones, minocycline and dapsone

Weenig et al. *NEJM* 2002;347(18)
Partridge et al. *Br J Dermatol* 2018;179(2)

Melanoma and Skin Tumors

2019 AAD Guideline Primary Cutaneous Melanoma

DIFFERENTIAL DIAGNOSIS OF PIGMENTED LESIONS

BENIGN—nevus (congenital, acquired), freckle, seborrheic keratosis, *café-au-lait*
PRE-MALIGNANT—dysplastic nevi syndrome
MALIGNANT—melanoma (superficial spreading, nodular, lentigo maligna, acral lentiginous), **pigmented basal cell carcinoma**

PATHOPHYSIOLOGY

RISK FACTORS OF MELANOMA

- **GENETICS**—fair skin/ethnicity, red/blonde hair, blue eyes, family history
- **NEVI**—number of common/atypical nevi (marker of sun exposure), familial dysplastic nevus syndrome, previous melanoma
- **EXPOSURE**—intermittent intense sun exposure, phototherapy, immunosuppression

HISTOLOGIC TYPE

- **SUPERFICIAL SPREADING** (70%)—fifth decade of life, both sexes, initial radial growth, common on back, posterior legs of women
- **NODULAR** (15%)—grows rapidly vertically. More common in men
- **LENTIGO MALIGNA** (10–15%)—sun-damaged skin, older patients, 5–20-year radial growth phase
- **ACRAL LENTIGINOUS**—most common melanoma in non-whites, who are at relatively lower risk for sun-exposure subtypes of melanoma. Affects palms, soles, and nails

CLINICAL FEATURES

DISTRIBUTION—more common on the trunk in men and extremities in women. Typically occur in relatively non-pigmented areas in non-whites. Unusual primary sites for melanoma include CNS, eyes, mucosa (respiratory, GI, GU), palate, gingival, vulva and anus

SYMPTOMS

- **LOCOREGIONAL**—skin lesion (see *JAMA* series below)
- **METASTATIC**—depending on location (lung, GI tract, liver, brain, subcutaneous, skin, bone, heart)
- **PARANEOPLASTIC**—vitiligo, melanosis syndrome (slate gray skin discoloration), dermatomyositis, gynecomastia, Cushing, hypercalcemia, neurological

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A MOLE OR A MELANOMA?
CHECKLIST ★ABCDE★—Asymmetry, **B**order irregularity, **C**olor variegation, **D**iameter >6 mm, **E**volution/**E**nlargement (change in lesion)
CHECKLIST FOR SUBUNGUAL MELANOMA ★ABCDEF★—Age, Black patients, Asians, and Native Americans, **B**rown to black band, **C**hange in the nail bed, **D**igit most commonly involved (great toe and thumb), **E**xtension of the pigment onto the nail-fold, **F**amily or personal history of melanoma
REVISED 7-POINT CHECKLIST—major: change in size or new lesion, change in color/

CLINICAL FEATURES (CONT'D)

irregular color, change in shape/irregular shape; minor: presence of inflammation, diameter ≥7 mm, crusting or bleeding, sensory change (sens 79–100%, spc 30–37%, depending on how many criteria used)

	LR+	LR–
ABCDE Criteria for Melanoma		
Asymmetry	2.1	0.59
Border irregularity	2.1	0.59
Color variegation	1.6	0.59
Dimension >6 mm	2.3	0.17
Enlargement	11	0.18
Combination of ABCDE Criteria		
5 positive findings	98	–
≥4 positive findings	8.3	–
≥3 positive findings	3.3	–
≥2 positive findings	2.6	–
≥1 positive finding	1.5	–
0 findings	0.07	–

APPROACH—using either checklist, misdiagnosing a melanoma as a benign lesion appears to be unlikely. The revised 7-point checklist has higher chance of classifying benign lesions as malignant. Non-dermatologists' examinations are less sensitive than those performed by dermatologists

UPDATE—combination of increasing ABCDE criteria increases the likelihood of melanoma; enlargement of a skin lesion is the single most powerful univariate predictor

Whited et al. *JAMA* 1998;279(9)
Simel et al. *The Rational Clinical Examination* McGraw-Hill; 2009

INVESTIGATIONS

BASIC

- **EXCISIONAL BIOPSY**—all lesions suspicious for melanoma should be biopsied with caution to obtain the total depth of the melanoma, with a 1–3mm margin of normal skin and some subcutaneous fat if possible. Breslow depth is the most important prognostic indicator

SPECIAL

- **LABS**—CBC, lytes, urea, Cr, LDH, AST, ALT, ALP, bilirubin as part of staging workup after pathology confirmation

INVESTIGATIONS (CONT'D)

- **IMAGING**—CXR as part of staging workup after pathology confirmation

DIAGNOSTIC AND PROGNOSTIC ISSUES

CLARK LEVELS (LIMITED UTILITY FOR SMALL LESIONS)

Level	TNM	5-year survival (%)
I	Intraepidermal (in situ)	100
II	Invasion into papillary dermis	95
III	Extensive invasion of papillary dermis	81
IV	Invasion into reticular dermis	68
V	Invasion into subcutaneous tissue	47

TNM STAGING

T stage (Breslow depth/thickness)

- **T1**—≤1 mm
  - **T1A**—<0.8 mm and without ulceration
  - **T1B**—<0.8 mm and with ulceration, or 0.8–1 mm with or without ulceration
- **T2**—1.01–2 mm
  - **T2A**—without ulceration
  - **T2B**—with ulceration
- **T3**—2.01–4 mm
  - **T3A**—without ulceration
  - **T3B**—with ulceration
- **T4**—>4 mm
  - **T4A**—without ulceration
  - **T4B**—with ulceration

N stage

- **N1**
  - **N1A**—one clinically occult node (i.e. detected by sentinel lymph node biopsy)
  - **N1B**—one clinically detected lymph node
  - **N1C**—microsatellite metastases ***and*** no regional lymph node
- **N2**
  - **N2A**—2–3 clinically occult node (i.e. detected by sentinel lymph node biopsy)
  - **N2B**—2–3 lymph nodes, at least one was clinically detected
  - **N2C**—microsatellite metastases ***and*** 1 clinically occult or clinically detected lymph node

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **N3**
  - **N3A**—≥4 clinically occult node (i.e. detected by sentinel lymph node biopsy)
  - **N3B**—≥4 lymph nodes, at least one was clinically detected, or presence of matted nodes
  - **N3C**—microsatellite metastases ***and*** ≥2 clinically occult or clinically detected lymph node, or presence of matted nodes

M stage (lungs, bone, liver, skin, and essentially any organ. Biologically heterogeneous with variable course)

- **M1A**—distant metastasis to skin, soft tissue or non-regional nodes
- **M1B**—distant metastasis to lung
- **M1C**—distant metastasis to non-CNS visceral sites
- **M1D**—distant metastasis to CNS sites

SENTINEL LYMPH NODE BIOPSY—usually done if primary melanoma is 1–4 mm thick or ulcerated

MANAGEMENT

PREVENTION—**sun avoidance** (sun-protective clothing, wide-brimmed hat, sunscreens)

SURVEILLANCE—particularly for high-risk individuals

STAGE I–III—standard of care is **wide local excision**. Mohs micrographic surgery may be used. Excision margin 1 cm for lesions ≤1 mm thick, 1–2 cm for lesions 1.01–2 mm, and 2 cm for lesions >2 mm thick). **Sentinel lymph node biopsy** for lesions >1 mm thick. If palpable node or sentinel lymph node positive, consider **lymph node dissection** and **adjuvant therapies.** For desmoplastic melanoma with high risk features, consider **adjuvant radiation**. Adjuvant therapy with ipilimumab, nivolumab, pembrolizumab, or dabrafenib plus trametinib results in substantial improvement in recurrence-free survival rates in patients with advanced-stage melanoma (stage III and IV) and is the new standard of treatment replacing adjuvant high-dose interferon α2b. For locoregional recurrence, consider re-excision

STAGE IV

- SURGERY—excision of solitary brain or lung metastasis is occasionally done, then treat as curable disease as above
- MUTATION TESTING—BRAF V600E/K. Mucosal and acral melanomas without a BRAF 600 mutation should be assessed for a KIT mutation

MANAGEMENT (CONT'D)

- PALLIATIVE SYSTEMIC THERAPY
  - FIRST LINE—consider nivolumab, pembrolizumab, or combined nivolumab and ipilimumab (preferred if BRAF mutant)
  - SUBSEQUENT LINES—BRAF and MEK inhibition (dabrafenib + trametinib, vemurafenib + cobimetinib) if BRAF mutant, imatinib if KIT mutant. Chemotherapeutic agents include dacarbazine, temozolomide, paclitaxel or carboplatin plus paclitaxel
- PALLIATIVE RADIATION—if localized pain
- PALLIATIVE CARE—referral for patients with supportive care needs

TREATMENT ISSUES

FOLLOW UP—should include a complete review of systems including headache, visual changes, cough, lymph node examination, and an LDH and imaging to rule out metastasis for patients with deep melanomas. Patients should continue skin examinations at least semi-annually for new lesions as patients have a 3–5% chance of developing another melanoma

SPECIFIC ENTITIES

DYSPLASTIC NEVI—acquired moles characterized by cytologic atypia and architectural disorder. They remain dynamic throughout life, constantly appearing, changing, or disappearing

DYSPLASTIC NEVUS SYNDROME—melanoma in ≥2 blood relatives and dysplastic nevi in other family members

BASAL CELL CARCINOMA

- PATHOPHYSIOLOGY—the most common form of skin cancer. Although they rarely metastasize, basal cell carcinomas are locally destructive and must be removed
- CLINICAL FEATURES
  - NODULAR SUBTYPE (50–80%)—pearly semitranslucent papules with telangiectasias and central depression; may ulcerate, crust, or bleed
  - SUPERFICIAL SUBTYPE (>15%)—psoriasiform scaly plaque; most common on trunk and extremities
  - PIGMENTED SUBTYPE (6%)—more common in Latin Americans and Asians
  - MORPHEAFORM SUBTYPE (2–6%)—white sclerotic plaque, can mimic a scar; predilection to recur
- RISK FACTORS—history of prior sunburns (especially in childhood), radiation therapy, family

SPECIFIC ENTITIES (CONT'D)

history, immunosuppression, fair complexion, and red hair
- **TREATMENTS**—usually treated by either excision or electrodessication and curettage. However, if superficial they may be treated with topical imiquimod or photodynamic therapy

ACTINIC KERATOSIS
- **PATHOPHYSIOLOGY**—form after chronic sun exposure in susceptible individuals usually on the face, scalp, forearms, and dorsal hands. Actinic keratoses are foci of superficial keratinocyte dysplasia capable of evolving into squamous cell carcinoma
- **CLINICAL FEATURES**—thin pink to red papules and plaques with overlying scale, may sometimes contain focal pigment. They are most common on people with fair skin (type I or II) and occur with increased frequency in patients who are immunosuppressed or have received phototherapy
- **TREATMENTS**—cryotherapy for focal lesions. If diffuse damage is present, one may use topical imiquimod, 5-fluorouracil, diclofenac, trichloroacetic acid peels, and photodynamic therapy. If there is a thick component below the skin surface, one should consider a skin biopsy to rule out underlying squamous cell carcinoma

SQUAMOUS CELL CARCINOMA
- **PATHOPHYSIOLOGY**—second most common form of skin cancer. On average 0.5–5.2% of squamous cell carcinomas metastasize, but they are much more aggressive on mucosal surfaces such as the lip and in areas of previous irradiation and scarring
- **RISK FACTORS**—same as risk factors for actinic keratoses, plus HPV infection for genital lesions
- **CLINICAL FEATURES**—typically firm red scaly plaques that frequently become ulcerated and occur in areas of heavy sun exposure in fair-skinned individuals. Subtypes include:
  - **BOWEN DISEASE**—squamous cell carcinoma in situ
  - **ERYTHROPLASIA OF QUEYRAT**—squamous cell carcinoma in situ of the penis
  - **KERATOACANTHOMA**—rapidly developing volcano-like nodule that may spontaneously involute
  - **VERRUCOUS CARCINOMA**—clinically and histologically resembles a wart
- **TREATMENTS**—surgical excision is the treatment of choice

SPECIFIC ENTITIES (CONT'D)

SEBORRHEIC KERATOSIS
- **PATHOPHYSIOLOGY**—benign tumor of keratinocytes. Generally familial in nature
- **CLINICAL FEATURES**—benign skin colored to black papules and plaques with well-defined borders. They often have a warty surface and a stuck-on appearance. Seborrheic keratoses are most commonly located on the back but can occur on the head, neck, and extremities. It is important to try to differentiate seborrheic keratoses clinically from melanoma. The Leser–Trelat sign denotes the sudden onset of numerous pruritic seborrheic keratosis along with skin tags and acanthosis nigricans and may indicate underlying malignancy (adenocarcinoma of the stomach and lung, leukemia, lymphoma, Sezary syndrome)
- **TREATMENTS**—liquid nitrogen cryotherapy, curettage, or shave removal

VERRUCA VULGARIS (COMMON WARTS)
- **PATHOPHYSIOLOGY**—a human papillomavirus (HPV) infection of keratinocytes. Lesions are benign but may cause cosmetic concern and are increased in immunocompromised individuals
- **CLINICAL FEATURES**—lesions are well-defined, firm papules or plaques with a hyperkeratotic cauliflower-like or flat surface. Lesions may have brown/black dots that represent thrombosed capillaries. Typically occur over extremities and genital area. Spontaneous resolution within 6 months for 30% of patients and 2 years for 65 % of patients
- **TREATMENTS**—manual paring of the lesions, cryotherapy, topical salicylic acid (e.g. salicylate cream 40% daily with glutaraldehyde 10–25% daily), imiquimod, 5-fluorouracil, cantharidin, podophylin, laser therapy, and intralesional bleomycin

VITILIGO
- **PATHOPHYSIOLOGY**—autoimmune process against melanocytes. Differential diagnoses include tinea, leprosy, morphea, lichen sclerosus, post-inflammatory hypopigmentation, and chemicals
- **CLINICAL FEATURES**—hypopigmented patch(es)
- **TREATMENTS**—topical steroids, systemic corticosteroids, topical calcineurin inhibitors, phototherapy

Cutaneous Lupus Erythematosus

DIFFERENTIAL DIAGNOSIS OF PHOTOSENSITIVITY

IATROGENIC (DRUGS)

- AMIODARONE
- DIURETICS—hydrochlorothiazide, loop diuretics
- ANTIBIOTICS—tetracycline
- **NSAIDS**
- ANTINEOPLASTIC—methotrexate, vincristine, 5-fluorouracil

INFLAMMATORY—SLE, dermatomyositis, rosacea

IDIOPATHIC—polymorphic light eruption, prurigo, actinic dermatitis, solar urticaria, chronic photosensitivity dermatitis

OTHERS—photocontact dermatitis, phytocontact dermatitis (celery, parsley, lime, lemon, yarrow), porphyria, xeroderma pigmentosum

CLINICAL FEATURES

CUTANEOUS MANIFESTATION OF SLE

- MALAR RASH—"butterfly rash" in up to 50% of lupus patients. Erythema in a malar distribution over the cheeks and bridge of the nose that spares nasolabial folds, especially after UV exposure
- DISCOID LUPUS—up to 50% of lupus patients. Discrete, erythematous, scaly plaques with follicular plugging over face, neck, and scalp, especially after UV exposure. May lead to central scars, atrophy, telangiectasias, and hyper-/hypopigmentation
- SUBACUTE CUTANEOUS LUPUS—up to 10% of lupus patients. Erythematous, slightly scaly papules that evolve into a papulosquamous or annular lesion over shoulders, forearms, neck, and upper torso. Usually no follicular plugging, hyperkeratosis, atrophy, pigment changes, and scarring
- LUPUS PROFUNDUS—firm, painful nodules over scalp, face, arms, chest, back, thighs, and buttocks
- LUPUS TUMIDUS—chronic violaceous papules and plaques or nodule lesions over areas exposed to the sun
- BULLOUS LESIONS—photosensitivity
- LIVEDO RETICULARIS—see SPECIFIC ENTITIES
- NAIL LESIONS—up to 25% of lupus patients. Changes include pitting, ridging, onycholysis and lunula (redness of half-moon), periungual erythema
- MUCOUS MEMBRANE ULCERS
- LUPUS ALOPECIA

INVESTIGATIONS

BASIC

- BLOOD TESTS—CBC, ANA, ENA, dsDNA

SPECIAL

- SKIN BIOPSY
- PORPHYRIA WORKUP—porphyrin, urine porphyrin

MANAGEMENT

TREATMENT UNDERLYING CAUSE—remove offending agent, sun protection. Topical steroid ointments and topical calcineurin inhibitors (tacrolimus) for localized cases. Antimalarials (hydroxychloroquine, chloroquine) for widespread cases. Systemic immunosuppressants or biologics for refractory cases

Borucki et al. ***Expert Rev Clin Pharmacol*** **2020;13(1)**

Related Topics
Systemic Lupus Erythematosus (p. 304)
Porphyria (p. 484)

SPECIFIC ENTITIES

CENTRAL FACIAL TELANGIECTASIA OR ERYTHEMA—common causes include rosacea, dermatomyositis, SLE, dermatitis (seborrheic, atopic, contact), glucocorticoid-induced dermal atrophy, flushing

TELANGIECTASIA—common causes include sun damage, aging, hypertension, alcoholism, diabetes, rosacea, amyloidosis, lupus, other rheumatic diseases, and ataxia telangiectasia

LIVEDO RETICULARIS

- CAUSES—**vascular** (polyarteritis, SLE, livedo vasculitis, cryoglobulinemia, antiphospholipid antibody syndrome, atherosclerosis, syphilis, TB), **hyperviscosity** (polycythemia, thrombocytosis, macroglobulinemia), **congenital**, **cerebrovascular disease** (Sneddon syndrome), **idiopathic**
- CLINICAL FEATURES—reddish-cyanotic, reticular patches over the arms, legs, and torso, particularly in cold environments. May progress to vascular occlusion with ischemia and tissue infarction (livedo vasculitis with triad of purpuric macules, cutaneous nodules, and painful ulcerations)

SPECIFIC ENTITIES (CONT'D)

PORPHYRIA CUTANEA TARDA

- **PATHOPHYSIOLOGY**—heterozygous deficiency of uroporphyrinogen decarboxylase, important for heme synthesis
- **ASSOCIATIONS**—hemochromatosis, alcohol, HCV, HIV, estrogens, smoking, hemodialysis
- **CLINICAL FEATURES**—photodistributed blistering or superficial skin erosion (commonly on back of hands)

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—avoid exacerbating factors (alcohol, smoking, estrogens, iron supplements, drugs). Phlebotomy to reduce ferritin <20 ng/mL is first line. Chloroquine, hydroxychloroquine. Avoid sunlight exposure until porphyrin levels are normalized

Drug Eruptions

DIFFERENTIAL DIAGNOSIS

EXANTHEMS

- **ANTIBIOTICS**—penicillins, sulfonamides, erythromycin, gentamicin
- **ANTICONVULSANTS**
- **ALLOPURINOL**
- **GOLD**

URTICARIA, ANGIOEDEMA

- **IMMUNE IGE-MEDIATED**—penicillins, cephalosporins, sulfonamides, local anesthetic agents, radiocontrast, transfusion, latex
- **NON-IMMUNE BRADYKININ-MEDIATED**—radiocontrast, ACE inhibitors
- **MAST CELL DEGRANULATION**—narcotics, muscle relaxants (atracurium, vecuronium, succinylcholine, curare), vancomycin

FIXED DRUG ERUPTION

- **LAXATIVES**—phenolphthalein
- **ANTIBIOTICS**—tetracyclines, sulfonamides, quinolones, penicillins
- **ANTI-INFLAMMATORIES**—NSAIDs, ASA
- **DIURETICS**—hydrochlorothiazide, loop diuretics
- **ANTI-NEOPLASTIC AGENTS**—methotrexate, vincristine, 5-fluorouracil
- **OTHERS**—barbiturates, antimalarials

ERYTHEMA MULTIFORME, STEVENS–JOHNSON SYNDROME ★4A'S★

- **ALLOPURINOL**
- **ANTIBIOTICS**—sulfonamides, penicillins, cephalosporins
- **ANTICONVULSANTS**—phenytoin, carbamazepine, phenobarbital
- **ANTI-INFLAMMATORIES**—NSAIDs

CONTACT DERMATITIS—neomycin, benzocaine, paraben, ethylenediamine, formaldehyde, para-aminobenzoic acid

DIFFERENTIAL DIAGNOSIS (CONT'D)

HYPERSENSITIVITY VASCULITIS

- **ALLOPURINOL**
- **DIURETICS**—furosemide, thiazide
- **ANTIBIOTICS**—penicillins, sulfonamides
- **OTHERS**—cimetidine, hydantoin

PIGMENTARY CHANGES

- **AMIODARONE**
- **ANTIBIOTICS**—tetracycline, minocycline, antimalarials
- **METALS**—silver, mercury, gold
- **OTHERS**—TCA, quinine, oral contraceptives

INVESTIGATIONS

SPECIAL

- **BLOOD TESTS**—CBC (eosinophils), quantitative Ig (IgE increased), tryptase (marker of mast cell degranulation)
- **ALLERGY TESTING**—radioallergosorbent test, patch testing
- **SKIN BIOPSY**

MANAGEMENT

DISCONTINUE OFFENDING DRUG—see SPECIFIC ENTITIES for further details

SPECIFIC ENTITIES

EXANTHEMATOUS DRUG REACTION

- **PATHOPHYSIOLOGY**—the most common type of cutaneous drug reaction. Common offenders include penicillins, sulfonamides, carbamazepine, allopurinol and gold
- **CLINICAL FEATURES**—exanthematous rash usually appears within 14 days of drug initiation or 3 days of re-offending drug. The reaction is characterized by the development of symmetric, red, morbilliform rash almost always found on the trunk and extremities, which may be very pruritic. Usually lasts 1–2 weeks

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—identification and cessation of the offending drug. Oral antihistamines for relief of itching. Topical glucocorticoids may speed up recovery. Oral and IV steroids may be used for severe symptoms

URTICARIA AND ANGIOEDEMA

- **PATHOPHYSIOLOGY**—urticaria involves the development of highly pruritic pink wheals. Angioedema is subcutaneous tissue swelling, most prominent on the face (lips, eyelids) and tongue
- **TYPES**—**IgE-mediated type I hypersensitivity reactions** occur within minutes to hours in sensitized patients and are classically associated with penicillin as well as cephalosporins and sulfonamides. Hypotension, bronchospasm, and laryngeal edema may accompany the rash. **Immune-complex mediated reactions** usually occur within 12–36 h of drug exposure in a sensitized individual. Common offenders are penicillins and immunoglobulins. **Non-allergic forms** of urticaria and angioedema occur from drug-induced bradykinin release and/or mast cell degranulation. The reaction typically occurs within 20–30 min of drug administration. Common drugs include NSAIDs, opiates, ACE inhibitors, calcium channel blockers, and radiocontrast
- **TREATMENTS**—cessation of the offending drug. Antihistamines and oral steroids may be used. For acute, life-threatening reactions, ABCs, O_2, ***epinephrine*** 0.5 mL of 1:1,000 (1 mg/mL) IM, repeat q5min as needed (consider epinephrine 0.01–0.02 mg/h IV for severe/refractory anaphylaxis), NS 1–2 L IV bolus, ***salbutamol*** 2.5 mg NEB q5min PRN, ***dimenhydrinate*** 25–50 mg IV, **steroids** (*methylprednisolone* 125 mg IV or *dexamethasone* 20 mg IV). Consider vasopressors if severe shock. **Consult** anesthesia if anticipate difficult intubation or ENT if urgent tracheostomy required

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

- **PATHOPHYSIOLOGY**—an acute, pustular eruption that typically begins in the body folds and/or face and spreads over the trunk and extremities
- **CLINICAL FEATURES**—diffuse, sterile pustules with an edematous, erythematous background. Patients may appear ill with fever and leukocytosis. Most cases begin within 2–3 days of drug administration

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—typically resolves within 2 weeks after the drug is stopped

FIXED DRUG ERUPTION

- **PATHOPHYSIOLOGY**—the appearance of a solitary erythematous patch or plaque within 30 min to 8 h after ingestion of a drug. Offending agents include antibiotics (tetracyclines, sulfonamides), analgesics (NSAIDs, salicylates), and yellow dyes
- **CLINICAL FEATURES**—erythematous, edematous plaques with a grayish center or bullae over genitalia (most common), lips, tongue, face, and acral areas. Characterized by presence of post-inflammatory hyperpigmentation and the recurrence at exactly the same site with reexposure. Lesions may be accompanied by itching or burning
- **TREATMENTS**—cessation of the offending drug and application of topical steroid ointment

CONTACT DERMATITIS

- **PATHOPHYSIOLOGY**—due to topical agents or contact. Type IV delayed hypersensitivity reaction causes allergic contact dermatitis. Non-immunological chemical or physical irritation causes irritant contact dermatitis
- **CLINICAL FEATURES**—erythematous, papular, urticarial, or vesicular pruritic plaques over area of exposure. Well-defined shape correlates with the offending contactant (e.g. nickel, tape, antibiotic ointment). Lichenification with chronic exposure
- **TREATMENTS**—identify and avoid causative agent(s). Emollients (irritant contact dermatitis) and topical steroids (allergic contact dermatitis) may alleviate symptoms

HYPERSENSITIVITY VASCULITIS

- **CLINICAL FEATURES**—macules/papules on lower extremities or back evolving into palpable purpura, bullae, and/or necrosis. May also have fever, myalgia, and arthralgia
- **ACR CRITERIA**—age at disease onset >16 years, medication at disease onset, palpable purpura, morbilliform rash, biopsy including arteriole and venule. Need 3 of 5 criteria (sens 71%, spc 84%)
- **TREATMENTS**—discontinue offending drug

Related Topics
Antibiotics (p. 270)
Penicillin Allergy (p. 274)

Erythema Nodosum

DIFFERENTIAL DIAGNOSIS OF PAINFUL NODULES

PANNICULITIS—erythema nodosum, erythema induratum, Weber–Christian disease (relapsing febrile nodular panniculitis)
INFECTIONS—bacteria, fungi
CUTANEOUS VASCULITIS
SUPERFICIAL THROMBOPHLEBITIS

PATHOPHYSIOLOGY

CAUSES OF ERYTHEMA NODOSUM

- **INFECTIOUS**—bacterial (streptococcal, yersiniosis), atypical (*Chlamydia pneumoniae*), TB, fungal (coccidioidomycosis, histoplasmosis, blastomycosis), leprosy
- **INFLAMMATORY**—IBD, SLE, Behçet
- **INFILTRATIVE**—sarcoidosis, Hodgkin lymphoma
- **IATROGENIC**—oral contraceptive pills, omeprazole, montelukast
- **IDIOPATHIC**

CLINICAL FEATURES

TYPICAL PRESENTATION—painful, erythematous nodules on the anterior surfaces of bilateral shins and sometimes thighs, trunk, and upper extremities. May evolve into bruise-like lesions that resolve without scarring over a 2–8-week period. Other symptoms include polyarthralgia, fever, and malaise. Presence of GI symptoms and/or hilar adenopathy may help in narrowing differential

INVESTIGATIONS

BASIC

- **LABS**—CBC, antistreptolysin-O titer, ANA
- **MICROBIOLOGY**—wound C&S, throat C&S (for *Streptococcus*), TB skin test
- **IMAGING**—CXR

SPECIAL

- **DEEP INCISIONAL BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE
SYMPTOM CONTROL—NSAIDs, potassium iodide, glucocorticoids (beware of TB)

Related Topics
Tuberculosis (p. 267)
Fungal Infections (p. 286)
Sarcoidosis (p. 483)

Clubbing

DIFFERENTIAL DIAGNOSIS

RESPIRATORY—lung cancer, lung abscess, bronchiectasis, cystic fibrosis, empyema, mesothelioma, idiopathic pulmonary fibrosis, asbestosis
CARDIAC—cyanotic heart disease, subacute endocarditis
GI—colon cancer, esophageal cancer, inflammatory bowel disease, celiac disease, cirrhosis
OTHERS—hyperthyroidism (thyroid acropachy), hemoglobinopathies, local vascular disease, familial

PATHOPHYSIOLOGY

MECHANISM—proliferation of the connective tissue between the nail matrix and the distal phalanx
STAGES—periungual erythema → spongy nail bed → loss of Lovibond angle → increased phalangeal depth ratio → hypertrophic osteoarthropathy

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE CLUBBING?
INSPECTION—**nail fold profile angle** (angle that nail projects from nail fold, normal $\leq$176°, simplified to straight line of <180° for clinical use), **hyponychial nail-fold angle** (angle that nail directs toward the nail tip, normal $\leq$192°, simplified to <190° for clinical use), **phalangeal depth ratio** (distal phalangeal finger depth/interphalangeal finger depth ratio normal $\leq$1), **Schamroth sign** (normal = diamond)
PALPATION—floating nail bed elicited by rocking the distal and proximal nail back and forth
APPROACH—if profile angle $\leq$176°, hyponychial angle $\leq$192° and phalangeal depth ratio $\leq$1, clubbing is unlikely. Inter-observer agreement of clubbing is highly variable among clinicians (κ 0.39–0.90). "The accuracy of clubbing as a marker of specific underlying disease has been

CLINICAL FEATURES (CONT'D)

determined for lung cancer (likelihood ratio, 3.9 with phalangeal depth ratio in excess of 1.0) and for inflammatory bowel disease (likelihood ratio, 2.8 and 3.7 for active Crohn disease and ulcerative colitis, respectively, if clubbing is present)."
UPDATE—clubbing in cystic fibrosis predictive of hypoxemia (LR+ 3.2)

Myers et al. *JAMA* 2001;286(3)
Simel et al. *The Rational Clinical Examination* McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **IMAGING**—CXR

SPECIAL

- **CARDIAC WORKUP**—ECG, echocardiogram
- **OTHER ETIOLOGY WORKUP**—CBC, TSH, AST, ALT, ALP, bili

MANAGEMENT

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

HYPERTROPHIC OSTEOARTHROPATHY—clubbing and periarticular pain and swelling, most often affecting the wrists, ankles, and knees. Associated with bronchogenic cancer, chronic pulmonary infections, cystic fibrosis, and cyanotic congenital heart disease

Related Topics
Celiac Disease (p. 142)
Inflammatory Bowel Disease (p. 140)
Lung Cancer (p. 205)

Dupuytren Contracture

DIFFERENTIAL DIAGNOSIS

DIABETIC CHEIROARTHROPATHY (usually all four fingers)
INTRINSIC JOINT DISEASE
DUPUYTREN CONTRACTURE
VOLKMANN ISCHEMIC CONTRACTURE
TRAUMATIC SCARS
PALMAR FASCIITIS—malignancy (usually bilateral)

PATHOPHYSIOLOGY

RISK FACTORS—alcoholism, smoking, diabetes, repetitive hand motions/vibrations, reflex sympathetic dystrophy, positive family history, Scandinavian/Northern European descent. Most patients are over 50 years of age.
4 STAGES—progressive fibrosis of the palmar fascia → nodules form on the palmar fascia → flexion deformity → fibrosis of dermis leads to skin thickening

CLINICAL FEATURES

HISTORY—finger stiffness (duration, pain, function), past medical history (alcohol, diabetes, smoking, HIV), occupational history
PHYSICAL—most commonly involves the fourth and fifth digits. Triangular puckering of the dermal tissue over the flexor tendon just proximal to the flexor crease of the finger (earliest sign), skin blanching on active finger extension, palpable and visible nodules along flexor tendons, mild tenderness over nodules, fixed flexion contractures, reduced range of motion, tender knuckle pads over the dorsal aspect of the PIP joints

MANAGEMENT

SYMPTOM CONTROL—padded gloves, stretching exercises for mild disease. Triamcinolone or lidocaine injection for moderate disease. Radiation, needle aponeurotomy, collagenase injection or surgery (fasciotomy or fasciectomy) for severe disease