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John J. Russell
Edward F. Ryan Jr. *Editors*

Common Dermatologic Conditions in Primary Care

Humana Press

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To my colleagues, past and present, who helped contribute to this book, thanks so much for your friendship and all that you have taught me through the years.
To Elena, Dana, Erin, and Paul, thanks for all your love and patience. You make everything possible.

– John

I would like to thank my wife, Jane, who has been supportive of my career, and I would also like to thank my coeditor John Russell MD who coordinated this effort and was the driving force in this project.

– Edward F. Ryan Jr.

Series Editor Introduction

Competent treatment of dermatologic conditions is critical to the practice of primary care. It has been estimated that almost three-quarters of all of the dermatologic care provided in the United States is provided by primary care clinicians, which include family doctors, internists, and pediatricians as well as primary care nurse practitioners and physician assistants. *Common Dermatologic Conditions in Primary Care* addresses the critical knowledge needs of these clinicians in an easy-to-read and reference format.

Common Dermatologic Conditions in Primary Care by Drs. John Russell and Edward Ryan is an important addition to the dermatology literature written collaboratively by a skilled dermatologist and an experienced academic family physician. As such, the book perfectly targets the depth and scope of need of primary care physicians in the field of dermatology.

It provides an in-depth discussion of the most common skin conditions that primary care physicians encounter and can be read through as a review of dermatology by interested clinicians or can be kept on the shelf to be used as a reference when an update on diagnosis and treatment is needed while taking care of patients. If a physician knows the contents of this book, he or she will be able to competently take care of greater than 90% of the dermatologic problems that are seen in a busy office practice.

That is an accomplishment.

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Approach to a Dermatologic Condition in Primary Care

John J. Russell and Edward Ryan

A large percentage of patients with dermatologic conditions present to a primary care clinician [1]. Most of these cases are not referred on to a dermatologist. A study in a primary care office found that approximately 85% of patients were better from their condition 2 weeks after their visit [2]. Therefore, the primary care clinician needs to develop some skills in approaching the evaluation and management of patients with dermatologic complaints. So how is this skill learned? The majority of medical schools in the USA do not require dermatology as a mandatory rotation. The accreditaion council of grauate medical education (ACGME) does not require specific dermatology rotations in family medicine, internal medicine, or pediatric residencies but rather experiences with dermatologic conditions [3]. This book is put together with those learners in mind. The purpose of this text is to review the most common dermatologic conditions that the primary care clinician will see in the office with a therapeutic approach to diagnosis and treatment.

Approach to a Dermatologic Condition

Taking a History

Like every other condition we see in our offices, history can be critical to making an accurate diagnosis. Dermatologic conditions are no different. The use of a more methodical history can help the clinician narrow their differential and make an accurate diagnosis.

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Onset

Try to accurately assess when the condition began. If it is a more chronic condition, how often does the patient have exacerbations? How long are these exacerbations, and how have they resolved in the past? This approach, combined with the intrinsic demographics of the patient, their age, sex, and other medical conditions, can help narrow the differential.

Evolution of the Disease Process

Ask your patient how their condition began. It can be helpful to have them point if the process has multiple lesions: which lesion was the first and how the lesions have progressed. It can also be helpful to look at the lesion that the patient identifies as the most recent. Are there lesions in different stages of evolution? How the condition finds itself distributed on the patient's body can be critical to making a diagnosis. Are there specific dermatologic symptoms associated with the condition? Is there pruritus present? If it is present, how severe is the itch? Is there a diurnal pattern to the itchiness? Is the lesion painful? What is the quality of the pain? How severe is the pain? Has the lesion changed over time? Is there bleeding of the lesion?

Associated Conditions

Does the patient have acute symptoms associated with the rash? Is the patient well or unwell upon presentation? Does the patient have concomitant fevers, chills, or myalgias with the condition? Does the patient have any other medical conditions? Is this condition stable or in flux? What medications does the patient take for this condition? Are any of these medications new or recently changed in dose? These factors can help the clinician decide if this is an acute cutaneous problem or if it part of a systemic disease state.

Provoking Factors

It is important to find out if their skin lesions were precipitated or aggravated by external factors. In the case of conditions like sunburn, this history narrows the differential immediately. One should remember though that many dermatologic conditions can be affected by factors such as sun exposure, extremes of temperature, foods, or medications. Has the patient been out of doors? If so, was the patient

exposed to bug bites, pool and hot tubs, or plants. What was the patient doing before he/she developed his/her acute condition?

Self-Medication

As much as any other condition, the patient often feels comfortable treating conditions on their own. There are low-potency topical steroids and antifungals available over the counter that patients may try. Taking a history of other prescription medications used with the disorder, either past prescriptions or borrowed from another patient, can significantly impact how a rash might present in the office. There is also a laundry list of home remedies that a patient might apply which can range from being helpful to disastrous.

Past Medical History/Family History

Taking an accurate personal and family history can help a great deal in determining the cause of a dermatologic problem. Many chronic diseases have dermatologic manifestations such as lupus or celiac disease. Many conditions run in families like atopic dermatitis or ichthyosis. Conditions like malignant melanoma are far more common in patients with a first-degree relative with the disorder.

Evaluating a Dermatologic Lesion

A good start to evaluating a skin lesion is becoming familiar with an accurate description of primary skin lesions. It is far more accurate to describe a lesion as a "macule" or "papule" that uses descriptive term like "macular" or "papular." It is important to be able to recognize a primary lesion and describe it in the chart or in describing the lesion to a colleague. Are there secondary lesions? Does their appearance differ from the primary lesions? How is condition distributed in the body? Does it involve the palms and soles of the patient? Also how is lesion configurated? This would include lesions being described as "annular," "linear," or "clustered."

Types of Primary Lesions [4]

- *Macule*: An alteration in skin color less than 1 cm in size without any elevation or depression of the adjacent skin (Fig. 1)

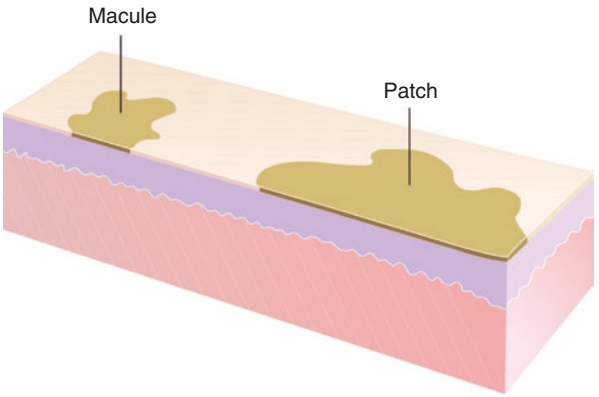

Fig. 1 Macula and patch. (From Wikimedia Commons – by Madhero88 – own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=14546457)

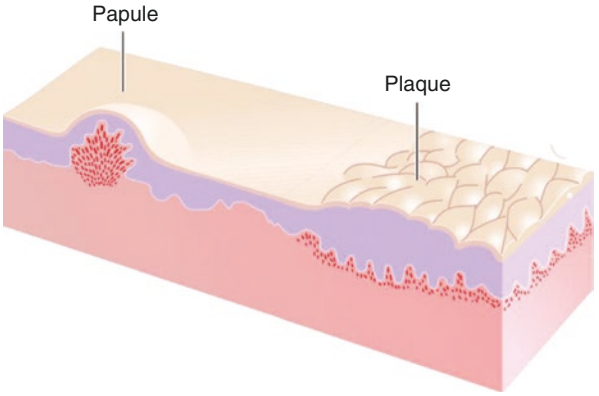

Fig. 2 Papule and plaque. (From Wikimedia Commons – by Madhero88 – own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=14546485)

- *Patch*: An alteration in skin color greater than 1 cm in size without any elevation or depression of the adjacent skin (Fig. 1)
- *Papule*: A solid skin lesion less than 1 cm raised above the surface of the adjacent skin (Fig. 2).
- *Plaque*: A lesion with significant diameter that has some elevation, but it is insignificant in relationship to its diameter (Fig. 2).
- *Nodule*: A solid skin lesion greater than 1 cm that may or may not be raised above the surface of the adjacent skin but might have more depth (Fig. 3).
- *Vesicle*: A circumscribed fluid-filled skin lesion less than 0.5 cm in diameter that is usually elevated above the skin surface (Fig. 4).
- *Bulla:* A circumscribed fluid-filled skin lesion greater than 0.5 cm in diameter elevated above the skin surface (Fig. 4).
- *Pustule*: A circumscribed fluid-filled skin lesion less than 0.5 cm in diameter that is usually elevated above the skin surface. The fluid contains purulent material.

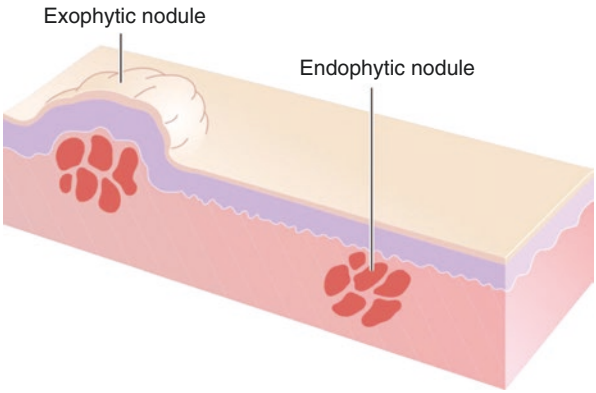

Fig. 3 Two types of nodules. (From Wikimedia Commons – by Madhero88 – own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=14546471)

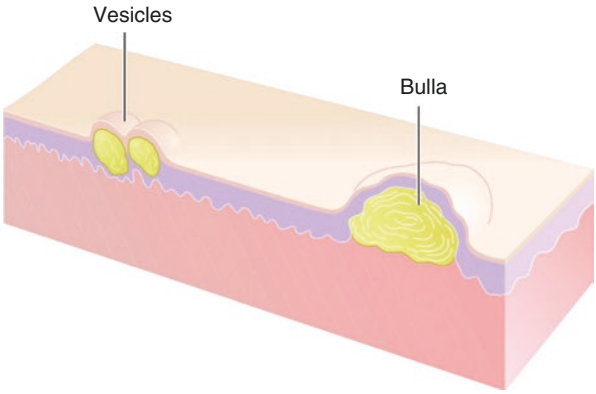

Fig. 4 Vesicle and bulla. (From Wikimedia Commons – by Madhero88 – own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=14546567)

Secondary Lesions

- *Scale:* A normal piece of stratum corneum that is a signal of abnormal epidermal maturation. Scale might be described by color, adherence, or texture
- *Crust*: An accumulation of exudate and/or blood.
- *Eschar:* An area of crust with tissue necrosis that will lead to scarring
- *Excoriation:* Areas of self-excavation that results in itching
- *Fissures:* Thin splits in the epidermis that are not caused by trauma (Fig. 5)
- *Erosion*: A moist, shallow depression that is the result of a loss of epidermis (Fig. 5).
- *Ulcer*: A loss of dermis and epidermis that will heal with some scarring (Fig. 5).
- *Hypo-/Hyperpigmentation*: A change in pigmentation of the skin that is caused by either depletion or excessive melanin deposits.

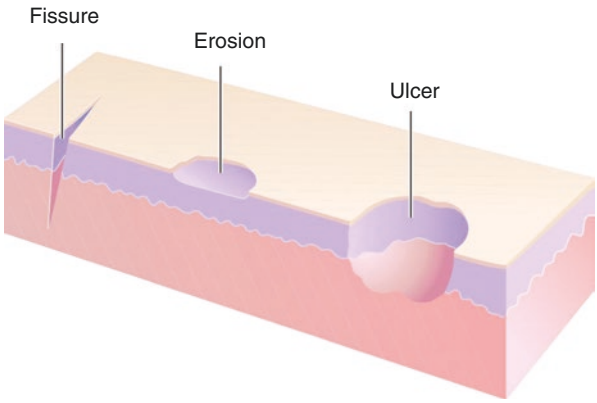

Fig. 5 Fissure, erosion, and ulcer. (From Wikimedia Commons – by Madhero88 – own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=14546561)

Fig. 6 Dermatoscope

Overall Evaluation of a Dermatologic Condition

Besides the use of the nomenclature above, the clinician should describe the lesions and include description of color, warmth, and texture. These can be added by proper lighting and using magnification. These can be done simply with handheld magnifier or through use of dermoscopy as described later in the book (Fig. 6). Vascular lesions may be assessed through diascopy. This is done through compression of a lesion through compression with a clear glass slide or its equivalent. Vascular lesion should empty and disappear with this compression, while solid lesions will remain in place. A portable ultraviolet lamp such as a Wood's lamp is especially helpful in pigmentary conditions and some tinea infections.

General Concepts of Treatment of Dermatologic Conditions

In using topical therapies, there are many things to keep in mind. Where on the body to use the preparation? Areas such as the face and groin have high percutaneous absorption of topical therapies, whereas areas like the palm and soles, knees, and elbow have very low absorption. Areas where the skin has fissures or ulcers will have much higher absorption of medications than areas that have thick scale and crusting which will absorb far less. This also is important with children who have an overall greater absorption of topical agents such as corticosteroids. Using occlusive dressings or even plastic diapers will increase the absorption. For medications such as topical corticosteroids, this is critical in choosing agents to use.

Vehicles

In choosing a therapeutic agent, it is important to decide which vehicle to use to deliver the treatment. *Gels* are best used in hair-bearing areas where the epidermis is thickest. They often sting because of the high alcohol content. *Ointments* are composed primarily of simple vehicle ingredients like petrolatum. This makes them very well tolerated with regard to burning or stinging with application. They are often "greasy" and are best used on dry skin lesions. They can lead to staining of clothing. *Creams* are more cosmetically elegant and rub in more fully. They can be more soothing to irritated skin. They are overall weaker than products using ointments as the delivery vehicle. They can be used in most areas except areas with dense hair. They can often be drying, so they might be chosen for more moist areas such as intertriginous areas. *Lotions* are liquid products that are mostly made of alcohol. They are best for hair-bearing areas like the scalp.

Topical Steroids

Topical corticosteroids are the mainstay of therapy for a variety of dermatologic conditions. They are categorized into seven different groups by potency (Table 1). The Group I steroids are the most potent products, and the Group VII are the weakest. Areas of high skin permeability such as the face and anogenital areas should use Group VI or VII steroids. Thicker areas of the skin like the palms and soles might require Group I products to achieve efficacy. Where a product is placed in the group might be related to the vehicle. For instance, triamcinolone acetonide 0.1% ointment is Group III, while triamcinolone acetonide 0.1% cream or lotion is Group V. Steroids should be selected to achieve efficacy with the lowest potency. Topical steroids can lead to local changes in pigmentation, rosacea, and skin atrophy and some systemic effects with very high doses over prolonged periods.

Table 1 Selected steroids by potency [5]

Aclovate Synalar Locoid			
Medication	Brand	Strength	Vehicle
Class 1 – very high potency			
Augmented betamethasone dipropionate	Diprolene	0.05%	Ointment
Clobetasol propionate	Temovate	0.05%	Cream, oint, gel, lotion
Halobetasol propionate	Ultravate	0.05%	Cream, oint, lotion
Class 2 – high potency			
Augmented betamethasone dipropionate	Diprolene AF	0.05%	Cream
Desoximetasone	Topicort	0.25%	Cream
	Topicort	0.05%	Gel
Fluocinonide	Lidex	0.05%	Cream, gel, oint, solution
Halcinonide	Halog	0.1%	Cream, oint, solution
Mometasone furoate	Elocon	0.1%	Oint
Triamcinolone acetonide	Kenalog	0.5%	Cream, oint
Class 3 – medium to high potency			
Amcinonide	Cyclocort	0.1%	Cream, lotion
Fluticasone propionate	Cutivate	0.005%	Oint
Class 4 – medium potency			
Betamethasone valerate	Beta-Val	0.1%	Cream, lotion
Desoximetasone	Topicort	0.05%	Cream
Fluocinonide	Synalar	0.005%	Cream, oint
Fluticasone propionate	Cutivate	0.05%	Cream, lotion
Mometasone furoate	Elocon	0.1%	Cream, lotion, soln
Triamcinolone acetonide	Kenalog	0.025%	Cream, oint, lotion
Class 5 – medium to low potency			
Hydrocortisone butyrate	Locoid	0.1%	Oint
Hydrocortisone probutate	Pandel	0.1%	Cream
Hydrocortisone valerate	Westcort	0.2%	Cream, oint
Prednicarbate	Dermatop	0.1%	Cream, oint
Class 6 – low potency			
Alclometasone dipropionate	Aclovate	0.05%	Cream, oint
Fluocinonide	Synalar	0.01%	Cream, soln, shampoo
Hydrocortisone butyrate	Locoid	0.1%	Cream, lotion, soln
Class 7 – lowest potency			
Hydrocortisone	Generic	1%, 2.5%	Cream, oint, lotion
Hydrocortisone acetate	Generic	0.5%, 1%	Cream

Amount of Topical Medication to Dispense

Dispensing the proper amount of medication is important for all the medications we use, and topical preparations are no different. One needs to balance expense, co-pays, patient convenience, and potential overuse/misuse leading to side effects. A 30 gram tube of cream covers the entire body of the average adult once. One gram

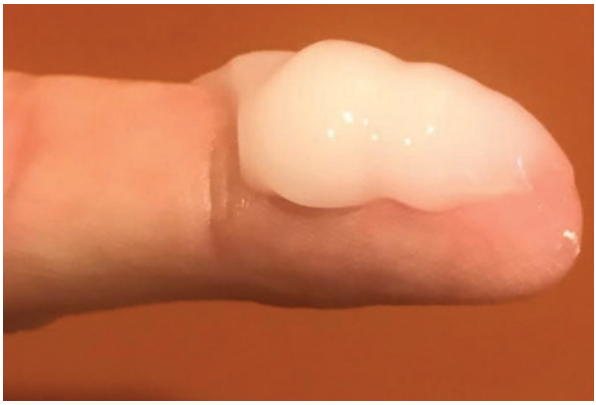

Fig. 7 Fingertip unit. (Photo courtesy author)

of cream will cover 100 square centimeters of the skin. To help calculate the amount to dispense, there are several methods for dermatologic preparations. A fingertip unit (FTU) (Fig. 7) is the amount of ointment squeezed out of a standard tube opening from the DIP crease of the finger to the tip. One FTU is roughly 0.5 grams of medication. A hand surface requires 0.5 FTU of medication or 1% of the body. One can use this to calculate the amount of cream or ointment needed multiplied by daily dosing (usually twice daily) and number of days.

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Common Newborn Dermatologic Conditions

Mark Ulbrecht and Gerard M. Cleary

Congenital Dermal Melanocytosis

Congenital dermal melanocytosis, previously referred to as Mongolian spots, is one of the more common neonatal dermatologic findings. Its prevalence differs greatly between races and ethnicities with one study reporting it affecting 40% of Asian, 32% of African American, 25% of Hispanic, and 6% of Caucasian newborns [1]. It is also associated with male sex and prematurity [2]. It is primarily found on the sacrum/buttocks but may occur elsewhere (Fig. 1). The most common extrasacral site is the lower extremities, making up 1% of cases [2], and even more rarely, they can be extensive [1]. Diagnosis is clinical and made by appearance of blue-gray (blue-green even) pigmented macule with indefinite borders. In the majority of cases, they will fade and even disappear over a few years, but it is important to document their presence as they may be confused with bruises. Features that predict more persistent lesions are having multiple lesions, extrasacral sites, diameter larger than 10 cm, and darker color [2]. In extensive, persistent, or progressive lesions, dermal melanocytosis may be associated with lysosomal storage disorders, and further investigation is warranted in these cases [3, 4].

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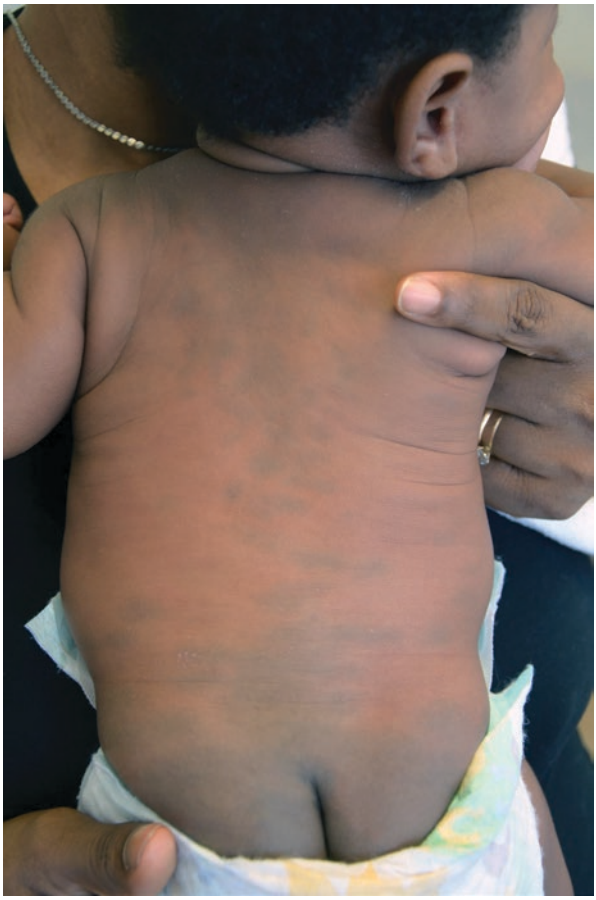

Fig. 1 Dermal melanocytosis – Wikimedia Commons

Erythema Toxicum Neonatorum

Erythema toxicum neonatorum is relatively common with reported prevalence varying from 7% to 16% [1, 5]. It is associated with Caucasian race, higher birth weights, greater gestational age, vaginal delivery, younger maternal age, and lesser gravida. It presents within the first 24–48 hours as flat, round erythema with a central papule or sterile pustule, primarily affecting the trunk and proximal extremities (Figs. 2 and 3). The diagnosis is clinical and based on a classic presentation without other concerning signs/symptoms [5]. The underlying mechanism is uncertain but may involve an immune reaction to hair follicles. No treatment is required as it is benign, self-limited (resolving within 1 week), and without

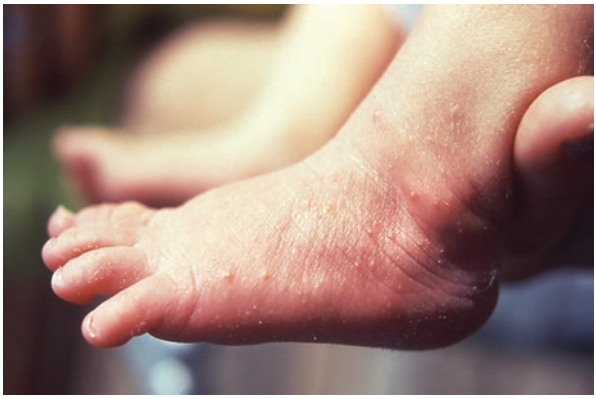

Fig. 2 Erythema toxicum – CDC/James Allen

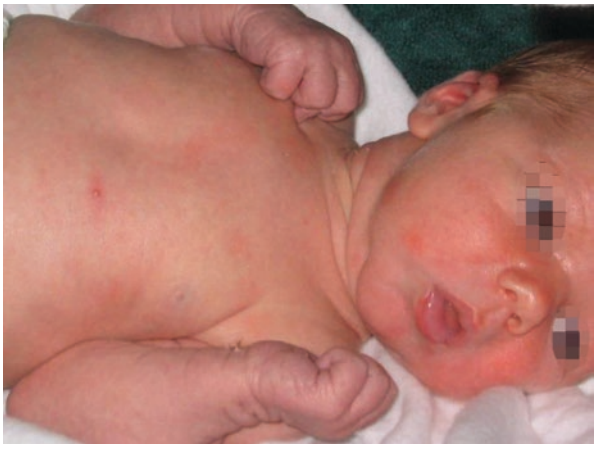

Fig. 3 Erythema toxicum – DermNet NZ

complications or sequela [6]. If the presentation is atypical, a pustule may be unroofed and fluid sent for analysis and culture.

Sebaceous Gland Hyperplasia and Milia

Sebaceous gland hyperplasia is perhaps the most common though underwhelming and completely benign newborn dermatologic finding. It appears as small, yellow or flesh colored, papules on the nose of an infant with an incidence of >40% and resolves within a few weeks. Maternal androgens are thought to play a part in its development [1]. Milia (Fig. 4), less common though similarly benign, are seen as pearly white 1–2 mm papules on the nose, cheeks, chin, and forehead, resolving within a few weeks [1].

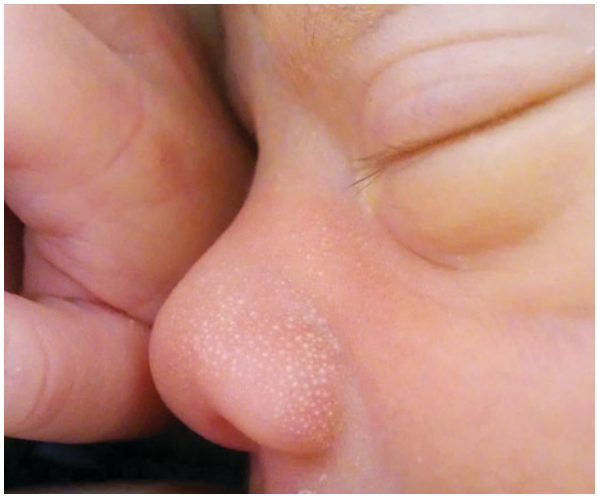

Fig. 4 Mila – DermNet NZ

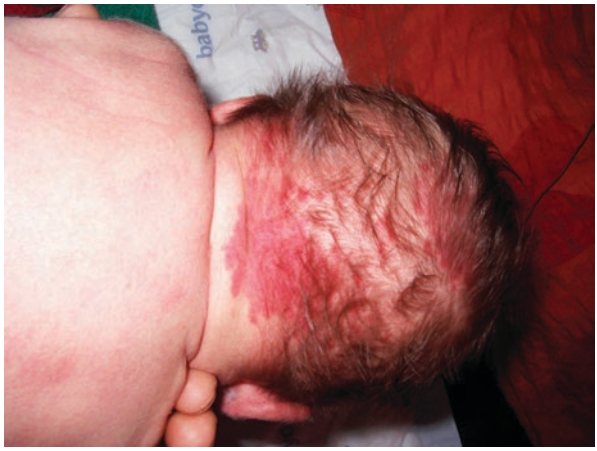

Fig. 5 Nevus simplex – "stork bite" by Wierzman – own work (selbst fotografiert), CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=10300541

Nevus Simplex

Nevus simplex – commonly referred to in lay terms as "salmon patch" generally or based on their anatomical position such as "stork bite" on the nape/occiput (Fig. 5) and "angel kiss" on the glabella or eyelid (Fig. 6) – is a benign capillary malformation. It is present at birth and is characterized as single or multiple blanchable, pink-red patches [7]. It has been reported, in one distribution or another, in upward of 83% of newborns. When present, it most commonly involves the nape/occiput, eyelids, and glabella in 54%, 23.1%, and 13.5% of cases, respectively, but may involve the nose, philtrum, legs, or lumbar areas [1]. If it is present in the lumbar area, it is recommended to further evaluate the spine with ultrasound

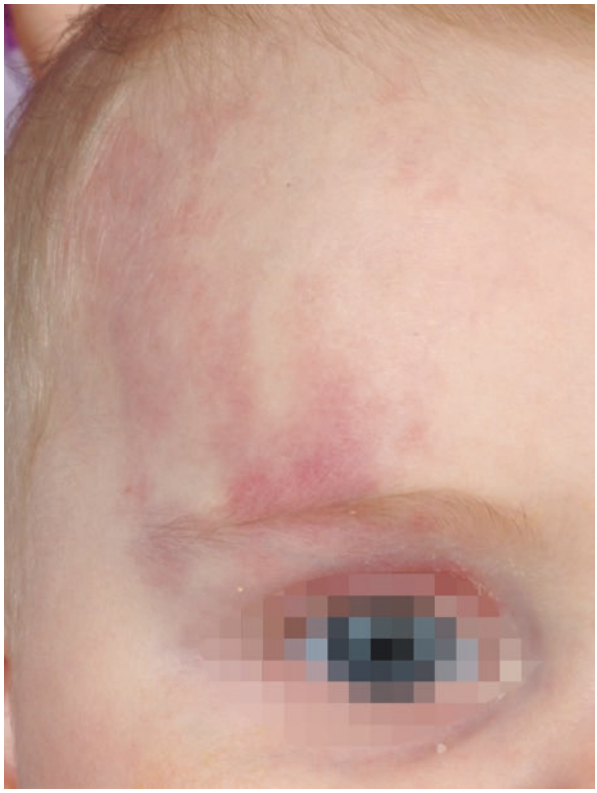

Fig. 6 Nevus simplex – "angel's kiss" – DermNet NZ

to assure it is not an outward sign of a deeper process [7]. Like many benign newborn rashes, the majority fades or disappears within the first few years.

Nevus Flammeus

Nevus flammeus – colloquially referred to as "port-wine stain" or "firemark" – must be differentiated from nevus simplex as it may be associated with syndromes involving the brain or development requiring close observation and may need further evaluation depending on their location. It is much less common with an incidence of only 0.3% [1]. Similar to nevus simplex, it is present at birth as a blanchable, pink-red patches; however, it tends to be unilateral, segmental, and not crossing the midline, and presents anywhere on the body (Fig. 7). Instances involving the ophthalmic (V1) trigeminal nerve distribution can be associated with Sturge-Weber syndrome (Fig. 8) and ipsilateral glaucoma. Unlike nevus simplex, it persists – even growing darker – and grows proportionally with the child. Given the potential and concern for disfigurement, laser treatment can be considered through evidence is preliminary at this time and shows improvement rather than resolution [8].

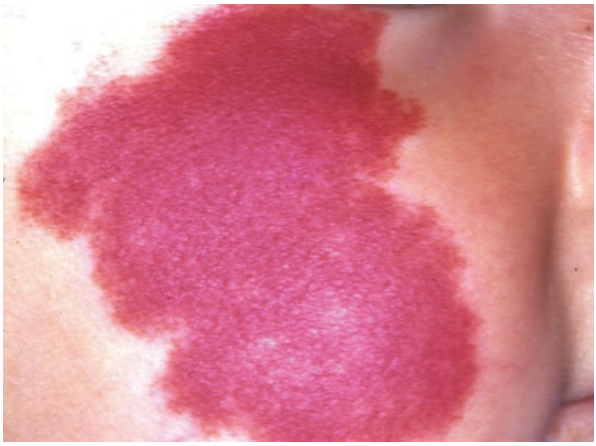

Fig. 7 Nevus flammeus – DermNet NZ

Fig. 8 Sturge-Weber – DermNet NZ

Infantile and Congenital Hemangiomas

Infantile hemangiomas (IH) are not generally apparent at birth and may just appear as an inconsequential papule or telangiectasia but will become evident within 1 month. With an incidence of about 4–5%, it appears as bright red macules, papules, or plaques if superficial or blue nodules if deeper (Figs. 8 and 9a, b). It is associated with prematurity, with development in almost 10% of premature infants in one study, as well as Caucasian race, female gender, and multiple gestations [1]. Most reach full maturity by 3 months of age with gradual involution by 4–6 years.

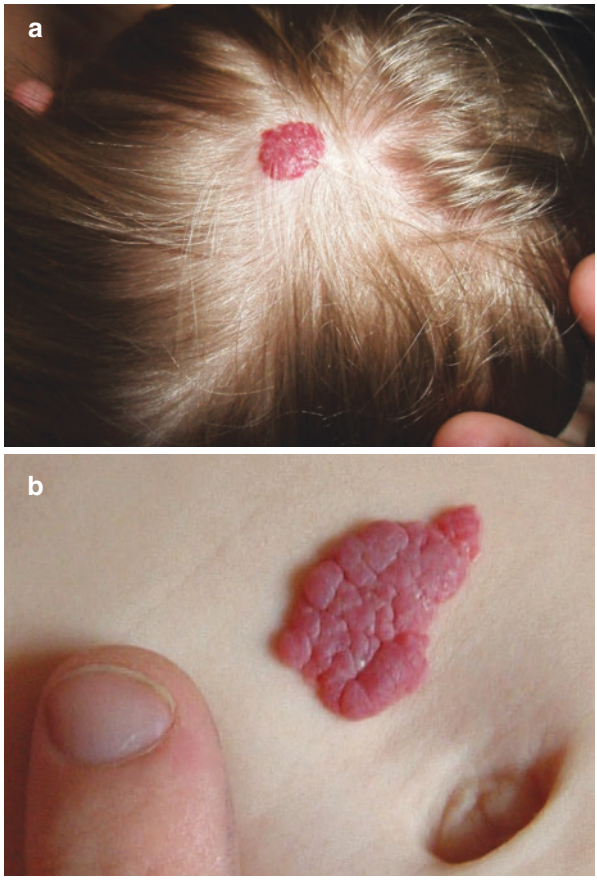

Fig. 9 (**a**) Infantile hemangioma – by Cbheumircanl – own work, public domain, https://commons.wikimedia.org/w/index.php?curid=12316343. (**b**) Infantile hemangioma – by User-Zeimusu – own work, public domain, https://commons.wikimedia.org/w/index.php?curid=1162701

Risk stratification tools have been developed utilizing size, location, and number of lesions. The most common complication is ulceration and bleeding (5–10% of cases), but with increasing size and number, the risk for other complication increases (including disfigurement, functional compromise, visual/airway compromise, PHACE – posterior fossa brain malformations, hemangiomas of the face, arterial anomalies, cardiac anomalies, and coarctation of the aorta) [9].

Congenital hemangiomas (CH) (Fig. 10) should be differentiated from infantile hemangiomas (IH). Congenital hemangiomas are relatively uncommon, 0.3% incidence in one study [1], and fully formed at birth. IH can be subcategorized as either rapidly involuting (RICH) or non-involuting (NICH). They primarily occur as plaques or exophytic masses on extremities or head and neck, though NICH tends to be flatter and less exophytic. The majority of RICH resolved by 14 months of age, leaving some redundancy of the skin, decreased elasticity, hypopigmentation, or persistent telangiectasias. NICH will persist and grow proportionally with the child and eventually may require resection [9].

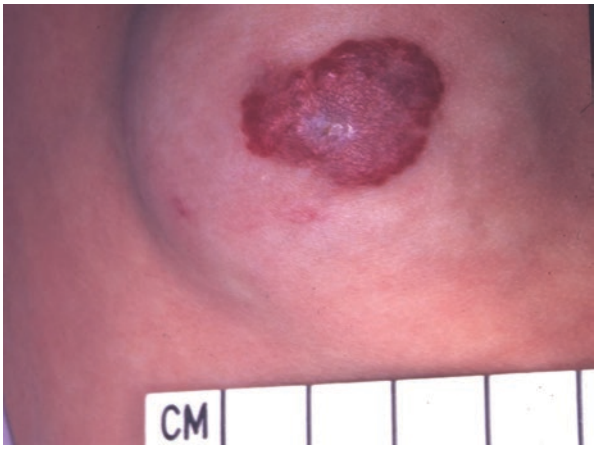

Fig. 10 Congenital hemangioma – DermNet NZ

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Childhood Exanthems

Michael Hurchick and Cornelia Winkler

The "childhood exanthems" were first classified over 100 years ago from First through sixth disease, which will be referred to as the classic childhood exanthems. The etiology of the term exanthem is Greek, meaning "to blossom out," in contrast to enanthems, meaning "to blossom in," and these refer to rashes of mucous membranes. We will review each of these disease entities, which were once very common in childhood and now mostly prevented by vaccination, as well as some more common exanthem presenting illnesses in children that one will likely see in the office. Although the classic childhood exanthems are mostly preventable, they remain ever important to our practices, as they are often not seen by many younger practitioners. Untreated, they can have deleterious side effects and complications. Outbreaks have been reported recently due to lack of immunization.

First Disease: Measles

Measles is one of the more pertinent exanthems today, considering recent outbreaks across the United States and Europe and its continued endemic status worldwide. Belonging to the *Paramyxoviridae* family, measles was first described in the seventh century. Although measles has a short survival time in air, or on objects, it is very virulent, spreading person to person via respiratory droplets. It is

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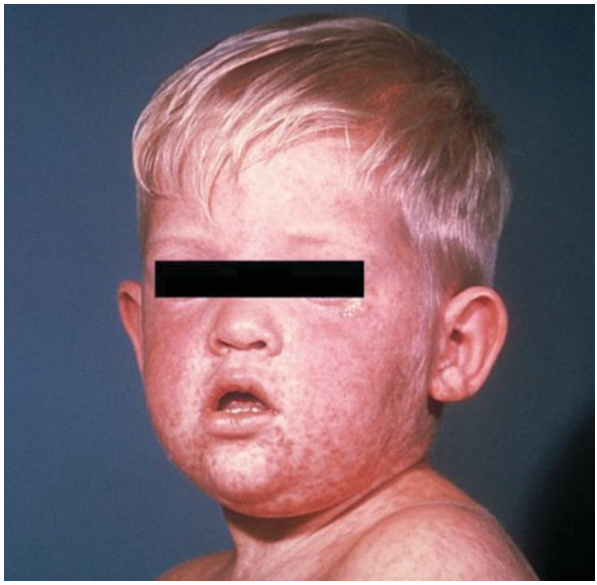

Fig. 1 Measles – CDC

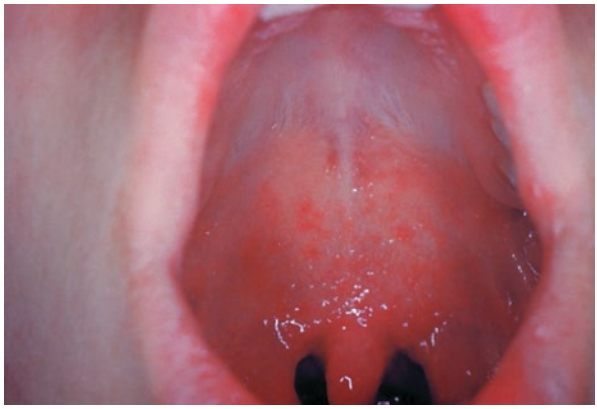

Fig. 2 Koplik spots in measles – CDC

more commonly seen in late Winter and Spring. The primary site of infection is nasal epithelium, which then spreads to local lymph nodes. Symptoms include the Classic 3 Cs (coryza, cough, and conjunctivitis), as well as fever and malaise. Diagnosis is generally clinical; suspicion should be high in low vaccine prevalence areas.

The rash generally occurs 14 days postexposure, beginning at the head and progressing toward the trunk and outward to the extremities (Fig. 1). It is described as maculopapular and erythematous with early blanching. Palms and soles are usually spared. The rash lasts roughly 5 days and will fade in a similar manner of presentation. The rash often progresses from purple lesions to copper toned lesions with fine scales [1]. Koplik spots are pathognomonic (Fig. 2), typically on the buccal mucosa,

and appear whitish to grayish on an erythematous base and often described as "grains of salt on a red background" [2].

Treatment is primarily supportive, which includes acetaminophen/ibuprofen and fluid replacement. Recent studies have shown vitamin A administration can decrease morbidity and mortality, possibly through increasing antibody production [3]. Measles is contagious generally from 4 days before to 4 days after rash appearance [6]. Complications can be severe (one in four is hospitalized), including subacute sclerosing panencephalitis, pneumonia, otitis media, diarrhea, and premature delivery in pregnancy [4]. Complications are more common in children less than 5 years of age and in adult patients [5]. Vaccination is the key to prevention.

Second Disease: Scarlet Fever

Scarlet fever, also known as scarlatina, is caused by an infection with Group A beta-hemolytic streptococcus, which is often found in nasal/oral cavity secretions, as well as on the skin. Infection may follow wounds, burns, URIs, and less commonly food poisoning. GABHS generally causes pharyngitis, commonly referred to a "strep throat." In a small percentage of those who develop a GABHS pharyngitis, scarlet fever develops. GABHS spreads via respiratory droplets. It is more commonly seen in Winter and Spring, as well as in the age group 1–10 [7], although up to 15 has been documented in literature. The rash itself is caused by the formation of erythrogenic toxin [8] from the bacteria. Symptoms often include pharyngitis, fever, and swollen tongue. Diagnosis is clinical. Strep tests can be performed to verify the presence of GAS. It may take scarlet fever up to 7 days of incubation [10].

The rash generally begins in the axilla and will spread to cover the trunk and then the extremities, sparing the palms and soles (Fig. 3). The rash will then desquamate, giving the feel of sandpaper. Pastia's lines are commonly seen; these are bright red markings in the creases of the body, namely, the axilla and groin. The rash is blanchable, diffuse, erythematous, and papular giving the skin the appearance and texture of sandpaper. Rash generally fades in 7 days [10].

Treatment of scarlet fever includes a 10-day course of penicillin, or amoxicillin. Patients can return to school/daycare after 24 hours of antibiotic treatment [9]. Complications are serious if untreated and include, but are not limited to, acute rheumatic fever, kidney disease, otitis media, and pneumonia.

Third Disease: German Measles/Rubella

Rubella, meaning "little red" in Latin, was first described by German physicians during the 1750s. It belongs to the *Togaviridae* family and was officially eliminated in the Americas in 2015 [11]. Its transmission is via respiratory droplets with replication in nasopharynx and regional lymph nodes. It was most common in late

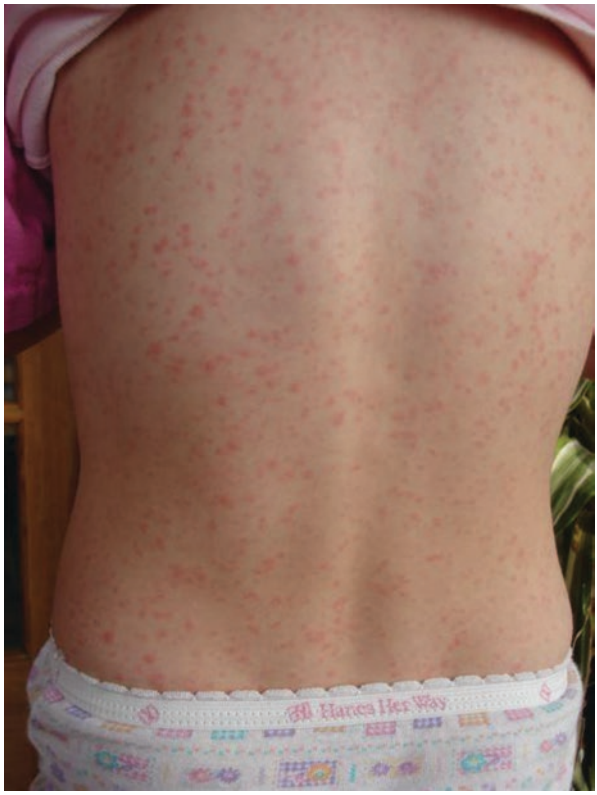

Fig. 3 Scarlatina – Permission – Alicia Williams Wikimedia Commons

Winter and early Spring. Incubation on average is 14–17 days. Symptoms are generally mild. The rash is generally first to appear and can be coupled with fever, malaise, lymphadenopathy (postauricular, posterior cervical, and suboccipital), URI symptoms, and arthritis. Laboratory diagnosis is only used for those suspected of having congenital rubella syndrome (CRS) and when complications arise thought to stem from rubella [14].

The rash appears typically 14 days after infection (Fig. 4). It is described as pruritic and maculopapular and generally progresses from head to foot. The duration of the rash is usually 2–4 days. It is most contagious between 7 days before and 7 days after appearance of the rash [12]. If a child is found to have rubella, he/she should be excluded from school and daycare for 5–7 days [13]. Again, vaccination is the key to prevention.

Overall, the treatment is supportive for rubella. Complications are rare; however, an infection in a pregnant patient can have devastating effects on a developing fetus. The impact of CRS is greatest in infections in the first and second trimester.

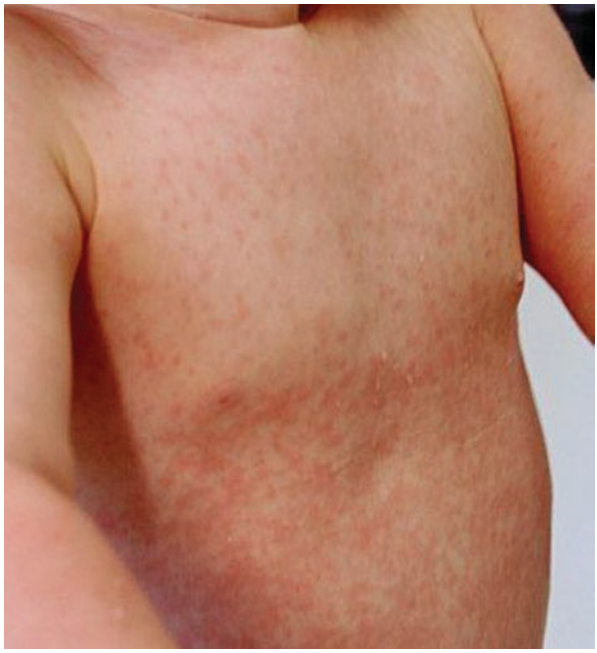

Fig. 4 Rubella – DermNet NZ

Fourth Disease

Also known as Dukes' disease, it is widely debated whether its etiology was a variant of scarlet fever or rubella. It is of no clinical relevance.

Fifth Disease: Erythema Infectiosum/Parvovirus B19

Erythema infectiosum is caused by parvovirus B19. It is transmitted via respiratory droplets, as well as via blood. Incubation to illness is 1–2 weeks [15]. Common symptoms are fever, URI, HA, nausea, and diarrhea [16]. Diagnosis is clinical.

The rash generally begins 2–5 days after the onset of symptoms. The facial rash commonly gives the appearance of having "slapped cheeks," which appear red, swollen, and warm, with circumoral pallor (Fig. 5). Often a reticulated, maculopapular rash manifests on the trunk and extremities and is pruritic in nature (Fig. 6). It usually remits after 7–10 days but can fade and reappear [16].

Treatment is supportive and aimed at relieving associated symptoms. Complications are rare in the immunocompetent pediatric population without

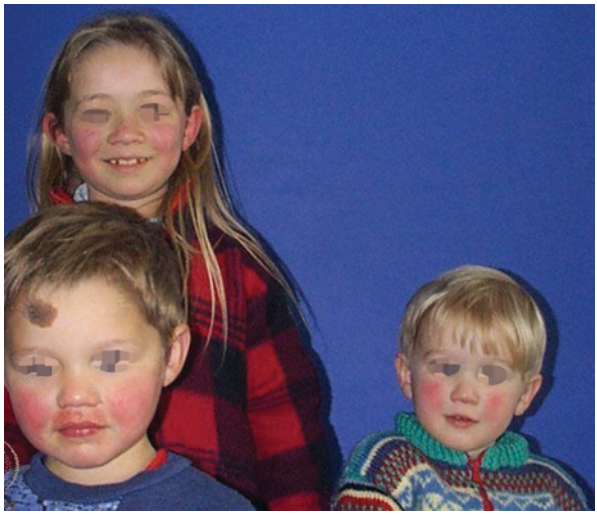

Fig. 5 Multiple children with fifth disease – DermNet NZ

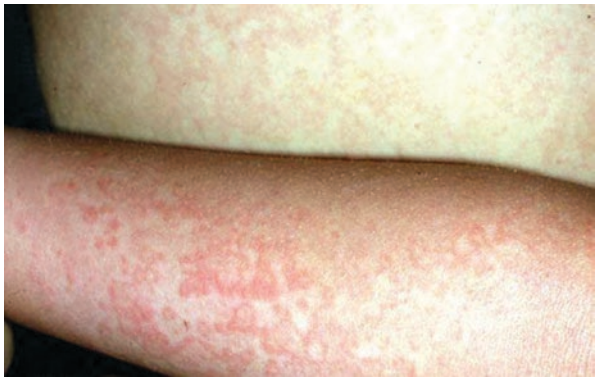

Fig. 6 Reticular pattern on the arm and trunk of fifth disease – DermNet NZ

underlying hematologic abnormalities but can be serious in the immunocompromised leading to anemia, as well as fetal death in those who are pregnant. One is no longer contagious once rash appears.

Sixth Disease: Roseola Infantum/HHV 6 and 7

Roseola infantum is generally caused by human herpesvirus (HHV) 6 and 7 and less commonly *Enterovirus* strains. It generally occurs in children less than 3 years of age [17, 18]. Transmission depends on the responsible etiological agent. For example, HHV 6 is transmitted by asymptomatic shedding in secretions of people in close contact and has an incubation period of 10 days [19]. Symptoms include high fever for 3–5 days, which can often exceed 104 F. Lymphadenopathy (cervical,

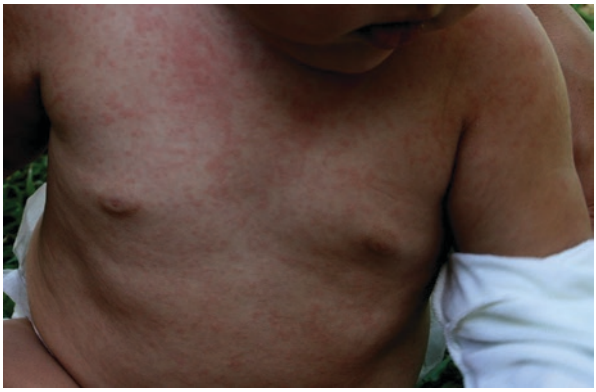

Fig. 7 Roseola – Permission granted – Emilia Burzagi

postauricular, and occipital), erythematous tympanic membranes, and irritability are common [20]. Overall, the diagnosis is clinical.

The rash (Fig. 7) follows after fever. It is commonly a blanching, maculopapular rash, which will begin at the neck, spreading down toward the trunk and upward toward the head. The rash can sometimes be vesicular. The duration of the rash is 1–2 days.

Treatment is supportive. There are no limitations to return to daycare/school [21]. Complications are rare; however, instances of seizures, aseptic meningitis, and encephalitis have occurred [20].

Other Common Childhood Exanthems

Lyme Disease

Lyme disease is caused by the spirochete *Borrelia burgdorferi*, which is carried in the saliva of the *Ixodes* tick. It accounts for over 90% of vector-borne illness in the United States [22]. A tick must be attached to the skin for 36–48 hours to cause to transmit the infection. Lyme disease presents in three stages: early localized, early disseminated, and late disease. Initial symptoms besides rash include fever, arthralgias, myalgias, and fatigue. Symptoms of early disseminated disease can include various neurological symptoms such as cranial nerve palsies and peripheral neuropathy, as well as cardiac findings, including a variety of atrioventricular blocks. Late Lyme disease manifestations include encephalopathy, arthritis, and other conditions.

During the early stages, the diagnosis is made clinically in areas endemic to the tick, or if patient's traveled to such an area who present with the typical EM rash (formerly erythema chronicum migrans). Serologic testing should be ordered for those patients who have traveled to or live in an endemic area and have a risk of exposure to ticks and display characteristics of early disseminated or late Lyme

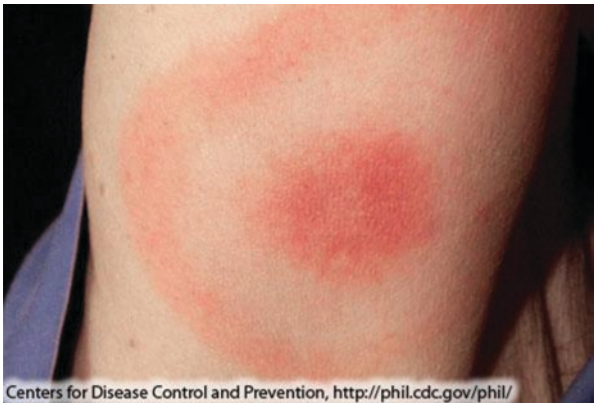

Fig. 8 Erythema migrans – CDC

disease [23, 24]. Antibodies against *B. burgdorferi* will not be detected for a few weeks after infection. Positive screening tests should be confirmed with a Western immunoblot. Treatment of early infection might prevent seroconversion.

The characteristic rash of Lyme disease occurs over exposed areas of the skin and is defined as the classical erythema migrans rash (Fig. 8). It is found in 70–80% of those infected [25]. The rash begins as erythema over the tick bite and expands around 16 centimeters from the center. Clearing may begin to occur inside the area of erythema, giving the classic bull's-eye rash of EM, as shown.

Those above 8 years of age may be treated with doxycycline 100 mg PO BID for 10–21 days. The treatment for children under 8 is amoxicillin 50 mg/kg per day (maximum of 500 mg/day) divided into three daily doses for 14–21 days or cefuroxime 30 mg/kg per day (maximum of 500 mg/day) divided into two daily doses for 14–21 days [26]. Doxycycline in children is avoided due to doxycycline's side effects, chiefly permanent tooth discoloration. Complications of untreated early Lyme range from early disseminated Lyme disease to late Lyme disease. Prevention is key. The use of insect repellents with DEET and covering limbs in tick-infested areas, as well as checking for and removing ticks promptly, are all important steps to reduce the likelihood of infection.

Hand, Foot, and Mouth Disease

Hand, foot, and mouth disease (HFMD) is usually caused by members of the enterovirus family, specifically Coxsackie A serotypes and enterovirus 71 [27]. It is spread through contact with bodily fluids, including saliva, vesicular fluid, and stool. It is more commonly seen throughout the Summer and early Autumn. Symptoms common to HFMD include rash, fever, malaise, abdominal pain, and herpangina. HFMD often occurs in those younger than 5 years of age [28]. Diagnosis is clinical.

Rash is variable in presentation (Fig. 9) but generally appears maculopapular, distributed on the feet, hands, buttocks, and groin with ulcers of the oral mucosa.

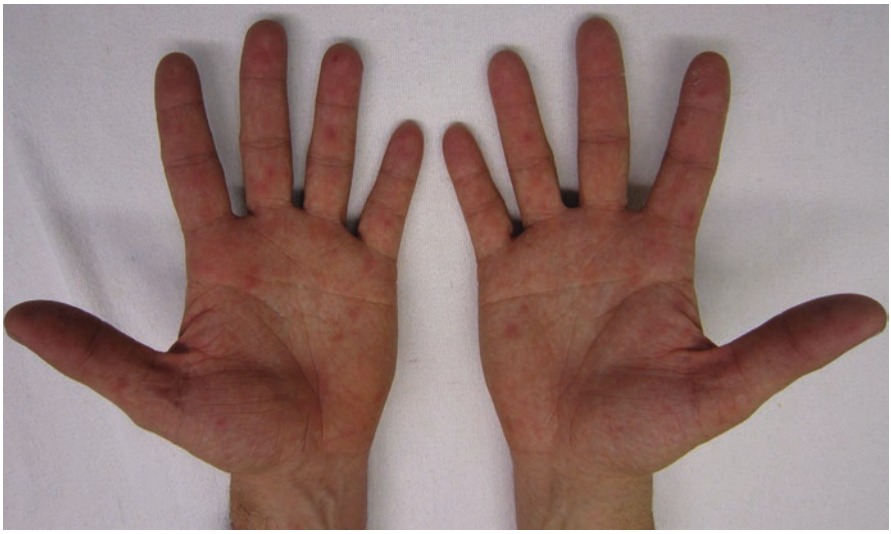

Fig. 9 Hands in Coxsackie infection with permission from James Heilman, MD

Fluid-filled vesicles are common and can erupt from the macules and papules. It is common to see macules, papules, and vesicles concurrently. The lesions are not often pruritic yet can be painful. The rash lasts for approximately 1 week. Of note, the oral enanthem starts as macules, which transition to vesicles and last to ulcers, often found on the faucial pillars, tongue, and buccal mucosa. In Coxsackie A6, nail dystrophy is known to also occur.

Treatment is supportive. Complications of HFMD are very rare but can range from dehydration, which may require hospitalization for IV fluid, to acute flaccid paralysis and aseptic meningitis. Resolution of HFMD occurs between 7 and 10 days [28]. HFMD transmission can be reduced by practicing proper hand hygiene, as well as cleaning surfaces exposed to bodily fluids. Children with active lesions should be kept home from school and daycare [29].

Varicella: Varicella Zoster Virus

Varicella, also known as chickenpox, was not reliably distinguished from smallpox until the nineteenth century. Varicella is a member of the herpesvirus family. Primary infection causes chickenpox, while reactivation of the infection will cause zoster or shingles. The highly contagious virus is transmitted person to person via respiratory secretions or from contents of vesicles. It can cause in utero infection through transplacental passage of virus. Entering through respiratory and conjunctival surfaces, it replicates in the nasopharynx and regional lymph nodes. The virus lives in sensory nerve ganglia. Symptoms begin 4–5 days after

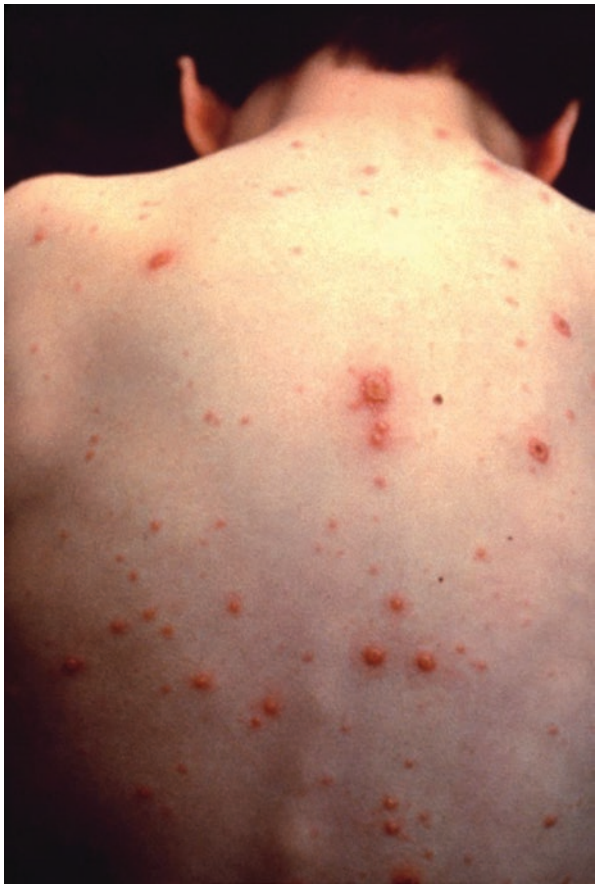

Fig. 10 Varicella lesions – CDC

inoculation, and incubation is 14 days postexposure [30]. Fever occurs before rash. Winter and early Spring are typical time for infection. Diagnosis is clinical in typical varicella presentations.

The rash begins on the head and spreads to the trunks and then extremities (Fig. 10). There can be mucous membrane involvement. The rash is pruritic and generally begins as macules and progresses to papules, and last vesicles, in varying stages.

Treatment is supportive. Antihistamines can be helpful for pruritus. Complications can arise, such as severe bacterial skin infections, pneumonia, and rarely meningitis and encephalitis. These are often more common in those younger than 1, older than 15, and the immunocompromised [31]. Antiviral therapy should be considered in patients at risk for severe disease. Varicella is generally infectious 1–2 days before rash appears and until the lesions have crusted. One should be excluded from school and daycare until no new lesions have appeared over 24 hours [31]. Vaccination is key for prevention for this condition as well.

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Atopic Dermatitis

Nandita Patnaik and Francesca Darquea

General Description and Epidemiology

Atopic dermatitis (AD), also known as atopic eczema, is a chronic, relapsing, pruritic, inflammatory skin disease which typically develops early in childhood [1–3]. In the United States, the estimated prevalence of eczema in children 0–17 years of age from 2009 to 2011 was 12.5%, an increase from 10.7% noted in 2003 [4, 5]. It is the most common chronic disease of children. Shaw et al. demonstrated that a higher prevalence, up to 18.1%, is found in patients 17 years and younger living in the East Coast states [5]. The percentage of affected children is shown to decrease with increasing age, 14.2% in 0–4 years as compared with 10.9% in 10–17 years [4]. In 90 percent of patients, atopic dermatitis will present by 5 years of age, and many have resolution of disease by adulthood [2, 3]. There is a characteristic distribution of lesions which corresponds to the age of presentation [2]. Infants will typically present with cheek, neck, scalp, trunk, and extremity involvement [6]. Early in childhood, the rash tends to present on flexural surfaces and the cheeks, while adolescent and adult patients often have rashes on the hands and feet [6] (Figs. 1 and 2). The hallmark clinical finding of atopic dermatitis is pruritus (Fig. 3). Other associated features may include xerosis, erythema, excoriations, serous exudate, and lichenification of the skin [2, 3] (Fig. 4).

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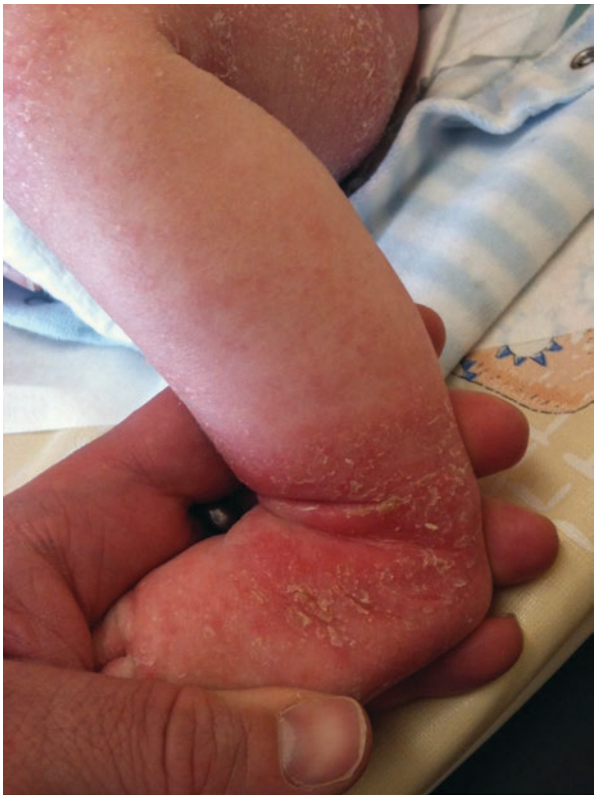

Fig. 1 Atopic dermatitis in a child. (By Gzzz – own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=46826115)

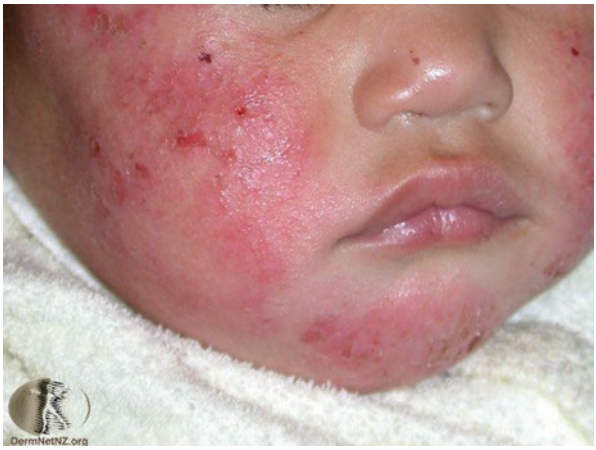

Fig. 2 Atopic dermatitis in infant. (DermNet NZ)

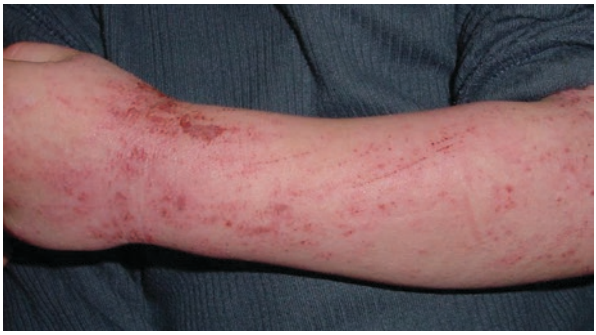

Fig. 3 Excoriated atopic dermatitis. (By the original uploader who was Eisfelder at German Wikipedia – transferred from de.wikipedia to Commons, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=3682825)

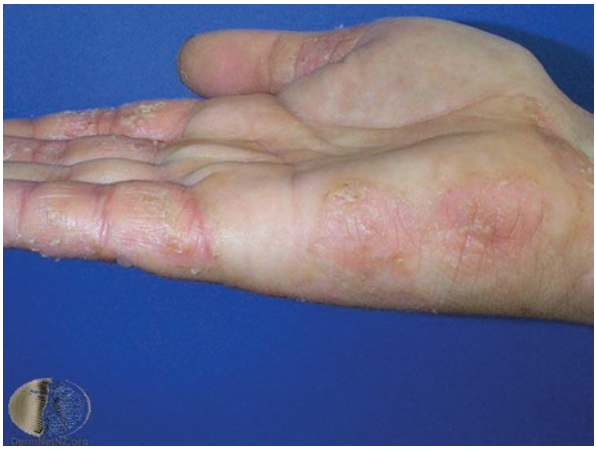

Fig. 4 Chronic hand eczema. (DermNet NZ)

Diagnosis

The well-known atopic dermatitis diagnostic standard, which includes 3 of 4 major and 3 of 23 minor criteria, was created by Hanifin and Rajka in the 1980s [3, 7]. Since that time, there have been many modifications offered by various international groups. In 1994, the UK Working Party diagnostic paradigm outlined one mandatory and five major criteria [8]. Following a consensus conference in 2003, the American Academy of Dermatology (AAD) suggested a revision based on the Hanifin and Rajka criteria [3]. An AAD working group's publication in 2013 then adapted the 2003 criteria for diagnosing AD in infants, children, and adults according to essential, important, and associated features [3]. Essential features include pruritus and the presence of eczematous lesions [3]. The list of differential diagnoses to consider includes contact dermatitis, scabies, seborrheic dermatitis, nutritional deficiencies (zinc/biotin), infantile psoriasis, and viral exanthems [2, 9].

Pathophysiology

The pathophysiology of atopic dermatitis (AD) has long been investigated yet is still not completely understood. Recent advances have highlighted abnormalities in the skin's structure and function, as well as localized inflammation and immunological changes in patients who possess a genetic predisposition to develop AD [2, 10].

It has been noted that the skin is the largest organ of the human body. According to Salmon et al., the "skin functions as more than a physical barrier: It is an active immune organ" [11]. The three layers of the skin (epidermis, dermis, and hypodermis) each play an important role in defending the human body from organisms and the environment. The latest atopic dermatitis research has focused on the epidermal barrier structure and function.

The outermost layer of the epidermis, the stratum corneum, is mainly responsible for its barrier function. It is composed of intracellular keratin filaments, intercellular lipids, and the cornified cell envelope [12]. The stratum corneum's integrity has been linked to appropriate expression of the filaggrin (FLG) gene [13]. This gene is responsible for encoding profilaggrin found in the stratum corneum [3]. Profilaggrin is a large protein which is cleaved into smaller filaggrin molecules [14]. Filaggrin is instrumental in aggregating keratin to form the cornified cell envelope layer that is critical to the barrier function of the stratum corneum and maintaining skin hydration [14]. FLG gene null and loss-of-function mutations as well as changes in copy number can contribute to a decreased expression of filaggrin and increase the risk of developing atopic dermatitis [10].

Tight junction proteins within the epidermal stratum granulosum layer create a second barrier to larger molecules in the skin by connecting neighboring cells to form a "paracellular barrier" [13]. The claudin family of tight junction proteins is most involved in the tightness and selectivity of this second barrier [13]. Changes in the molecular expression of tight junction proteins and desmosomes are linked to atopic dermatitis [2, 13].

Dysfunction of the skin's barrier then furthers the inflammatory and immunological processes associated with AD. The immune cells most involved in AD are the CD4+ T cells, including T helper (Th) cells, specifically Th1, Th2, Th22, and Th17 cells [10]. It has been shown that the mere presence of Th2 inflammatory cytokines may be responsible for weakening the skin barrier [2]. Interestingly, clinically unaffected areas of the skin in AD patients show baseline levels of inflammatory cells (Th2 and Th22), changes in the intercellular lipid arrangement, and increased cytokine release from keratinocytes [10, 15]. During an acute flare, Th2 and Th22 cytokine responses increase, and Th1- and Th17-dependent processes begin which leads to keratinocyte activation and release of pruritogenic and proinflammatory mediators in lesional skin [10]. Evaluation of chronic lesions demonstrates continued disruption of the epidermal barrier via the release of T helper cell cytokines, epidermal thickening, and local inflammation [10].

Another suggested mechanism for the development of AD involves the introduction of aeroallergens through a compromised skin barrier which triggers an inflam-

matory response [6]. Other research supports that the changes in the skin's level of hydration and subsequent increase in pH may activate proteases and kallikreins, thereby contributing to bacterial overgrowth, activation of the skin's innate immunity response, and the inflammatory cascade leading to AD [6, 16].

However, simply having a disrupted epidermal barrier does not lead to the development of AD. A strong family history of atopy is a known AD risk factor [3]. Twin studies show that roughly 80% of a person's susceptibility to developing atopic dermatitis is linked to their genes [17]. Mutations in the FLG gene have been noted as the greatest risk factor for developing AD, but these mutations are "neither necessary nor sufficient to cause atopic dermatitis" [1, 10]. Further research is necessary to elucidate the complex interactions, key molecules, and mechanisms of skin barrier dysfunction and immune and inflammatory responses that cause atopic dermatitis.

Treatment

Currently, there is no cure for atopic dermatitis, and mitigating symptoms is the mainstay of management [10]. The 2014 American Academy of Pediatrics Clinical Report by Tollefson et al. described the multi-pronged approach necessary in managing a patient's eczema: maintenance of a healthy skin barrier, itch control, infectious trigger avoidance, and application of topical anti-inflammatory medications [6].

Preserving the integrity of the epidermal barrier through the use of moisturizers serves as the foundation of treatment and prevention. Eichenfield et al. describe the three main ingredients of effective moisturizers (emollients, occlusives, and humectants) and their relevance to a healthy skin barrier [18]. Emollients are largely lubricants, while occlusives tend to serve as a barrier to water evaporation, and humectants attract water into the stratum corneum [18]. There are several types of moisture delivery systems available to AD patients. Typically, ointments are preferred over creams and lotions to improve the underlying xerosis, although patient and caregiver preference is often stressed to ensure compliance [9]. Ointments are thicker, often have a petroleum jelly base, and lack preservatives, while thinner creams contain some preservatives but are better tolerated by children attending school [2]. In contrast, lotions tend to have higher water content and additional chemicals that can contribute to further skin irritation [18]. Given adequate moisturizing is at the basis of treatment and prevention, it should be encouraged to occur at least twice daily regardless of the choice of moisture delivery system [10].

Arkwright et al. addressed the barrier and water retentive functions of the stratum corneum and the role of ceramides [19]. These lipids are diminished in AD patients [20]. Emulsions containing ceramide increase the epidermal lipid concentration and assist with decreasing transcutaneous water loss [19]. However, preparations containing ceramides have not been shown to be superior to other moisturizers [21].

Two randomized controlled trials, one based in the United Kingdom/United States and the other in Japan, evaluated the effects of moisturizers on the incidence of atopic dermatitis in high-risk neonates [22, 23]. Given that a family history of atopy is a strong risk factor for developing AD, recruitment in both studies was limited to these qualified participants [3, 22, 23]. Results from each trial demonstrated a statistically significant reduction in the onset of atopic dermatitis [22, 23].

Atopic eczema is commonly known as the itch that rashes. While many practitioners employ H1 receptor anti-histamines in an attempt to curb the itch-scratch cycle, the pruritus of atopic dermatitis results from the action of neuropeptides and the potent Th2 cytokine interleukin-31 [24]. Histamine 1 and 2 receptors have not been shown to be involved in the development of the itch of AD [25]. Of note, recent research of a novel histamine 4 receptor antagonist has been effective in treating the pruritus of AD in Japanese patients [26]. Oral H1 antagonists may have a role in minimizing trigger activation in patients with environmental allergies [27]. Other triggers that may cause pruritus include lotions, soaps, and detergents that are scented, rough or non-breathable fabrics, sweat, excess saliva, environmental allergens, psychosocial stress, and viral infections [6, 9, 10]. Given that each patient has unique triggers, it is imperative to perform a detailed history and skin prick or patch testing, if necessary, to assist in individualizing treatment plans [1, 6, 9].

Cutaneous infections are a frequent complication for patients with atopic dermatitis [6]. Two organisms commonly identified in relationship to AD are *Staphylococcus aureus* and herpes simplex virus (HSV) [28]. A large proportion of patients with AD are colonized with *Staphylococcus aureus* without clinical signs of infection. However, this colonization may lead to increased pruritus and worsening severity of AD [6, 18]. Patients with moderate to severe AD have shown improvement in severity using dilute bleach baths (0.005%) and concurrent intermittent intranasal mupirocin application [29]. Notably, topical anti-staphylococcal treatments are not recommended for routine use in patients with AD [18].

In addition to eczema herpeticum caused by HSV, AD patients are at increased risk of other viral illnesses leading to eczema coxsackium, eczema vaccinatum, and molloscum contagiosum [2]. Eczema vaccinatum is a sequela to the live vaccinia virus vaccine. The vaccine is contraindicated in those with AD and individuals with a close contact having AD [6]. Both eczema herpeticum and vaccinatum may present as serious life-threatening infections [28]. As the skin's barrier function is compromised in AD patients, prompt evaluation and treatment of cutaneous infections should occur.

Even with the best efforts to maintain a healthy skin barrier, the use of topical medications to treat skin lesions may be necessary given the pathogenesis of AD [6]. Patient and caregiver preferences, lesion location, regional availability, and cost are some factors taken into consideration when deciding on a topical medication [6, 9]. The first-line treatment of acute eczematous flares is topical corticosteroids which can decrease inflammation, pruritus, and bacterial skin colonization [2]. In the United States, there are seven classes of topical corticosteroids, stratified according to their potency. Class 7 medications are of the lowest potency, while Class 1 are noted to be 1800 times more potent and thus considered very high potency [6]. At the time of a patient's initial acute flare, the lowest-potency medication is started,

and the response to treatment is monitored within 1–2 weeks [9, 18]. Traditionally, if symptoms do not resolve with low-potency medications, then a higher-potency topical corticosteroid is employed. As low-potency topical corticosteroids do not carry many adverse effects, they are preferred in infants and children and for use on the face, neck, and intertriginous thinner skin areas [6, 10]. In severe flares, moderate-potency medications can be used, but caution is taken as inappropriate use can cause local and systemic side effects including skin atrophy, hypopigmentation, striae, telangiectasia, rebound flares, and adrenal suppression [2, 6, 9, 18].

A newer class of medications being used in moderate to severe AD is topical calcineurin inhibitors (TCIs). The mechanism of action of this class is based on selective inhibition of cytokine transcription in activated T cells [2]. The TCI side effect profile differs in comparison to higher-potency topical corticosteroids [6]. Known side effects of topical calcineurin inhibitors include stinging and burning which typically resolve in a few days [2]. Topical calcineurin inhibitors are more expensive than topical corticosteroids, which may be prohibitive for certain patients [6]. In February 2005, a Food and Drug Administration "black box" warning of increased malignancy risk was issued for TCIs [2]. A large study of 300,000 AD patients did not find an increased risk of lymphoma in AD patients treated with TCIs [1]. In the United States, both tacrolimus 0.03% ointment and pimecrolimus 1% cream have been approved for use in children greater than 2 years of age [2].

Other treatment modalities include wet wrap therapy [9], "proactive" application of topical medications [30], systemic immunosuppressant medications, biological agents, and adjuvant therapies [31].

Patient and caregiver education is crucial to effective treatment and control of symptoms [9]. Eichenfield et al. highlighted the importance of teaching the appropriate administration of topical medications and moisturizers [9]. The fingertip unit (FTU) is defined by Long and Finlay as the amount of ointment expressed from a tube with a 5 mm diameter nozzle, applied from the distal skin-crease to the tip of the index finger [32, 33]. This amount is sufficient to cover twice the area of an adult handprint, and 2 FTUs equate to 1 g of product [32, 33]. With the use of this metric, caregivers are better able to understand how much product to apply on patients and create an expectation of the amount of product to use in a defined period of time [9]. To assist with the educational aspects of care, the Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases (NIAID), at the National Institute of Health and other groups have created examples of eczema management plans based on symptom severity [2, 6]. Written treatment plans may lead to improved treatment adherence similar to the effectiveness seen with currently employed asthma action plans [6, 9].

Quality of Life

The impact on the quality of life of patients and caregivers is an important guiding principle in having adequate and appropriate treatment of AD. Sleep deprivation and fatigue as well as activity restriction and depression are contributing factors to

a poor quality of life for AD patients [6]. Patients with more severe disease burden can be at a higher risk of developing hyperactivity, anxiety, and other mental health disorders [34]. Parents and caregivers are also at risk of increased morbidity given that some may spend more than 2 hours per day caring for their children's skin [6]. Lack of sleep, fatigue, treatment-related financial expenditures, and feelings of hopelessness, guilt, and depression have been reported in many parents of atopic dermatitis patients [6].

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Contact Dermatitis

Katyrena Kiselova and John J. Russell

Introduction

Primary care physicians are often found on the front lines of diagnosing and treating dermatologic conditions. A common ailment that many family medicine physicians see is contact dermatitis. Although it may appear to have a simple etiology, the initial diagnosis and subsequent treatment can be difficult. With the chemical industry being on the rise, new allergens and irritants become the culprits of contact dermatitis.

Several sources cite the incidence of contact dermatitis as high as 10–20% of all dermatologic conditions [1]. Contact dermatitis affects people of various professions, age, and gender. Symptoms vary in severity; however, oftentimes, they can be lifelong and impact social and professional aspects of patients' lives. Thus, the knowledge of how to recognize, diagnose, and treat contact dermatitis becomes essential.

Contact dermatitis is a skin condition which develops due to exposure to either an irritant or an allergen. Thus, it is classified into two categories: irritant contact dermatitis and allergic contact dermatitis. Irritant contact dermatitis is the more common of the two, being responsible for approximately 80% of cases, while allergens cause 20% of cases [2]. Although both types are caused by an insult to the epidermal barrier, the pathogenesis is very different.

Stratum corneum is an important part of the skin's permeability barrier, which protects the dermis from chemicals, microbes, and mechanical assaults [3]. If the

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stratum corneum becomes disrupted, the skin becomes highly susceptible to outside insults. Skin lipids, corneocytes, and tight junctions such as occludin and claudin in the epidermis are the front lines of the skin permeability barrier [3]. Cytokine signaling plays a role in epidermal homeostasis and repair [3]. Chronic contact dermatitis can sometimes be attributed to an increase in cytokine production as a response to repair the epidermis [3].

Once skin barrier becomes damaged, allergens and irritants can penetrate easily.

Proksch and Brasch describe allergen-specific T cells being the most important differentiating factor between allergen and irritant contact dermatitis propagation. Irritant contact dermatitis is often a result of prolonged exposure to the irritant, such as water, soap, or detergents, whereas allergic contact dermatitis is a type IV delayed hypersensitivity reaction caused by re-exposure to an allergen after initial sensitization [4].

Prevalence and Etiology

Contact dermatitis can most commonly be attributed to occupational, cosmetic, or environmental exposure. Occupational exposure to a wide variety of chemicals is the typical setting in which contact dermatitis occurs. It accounts for over 70–80% of all occupational dermatologic conditions, and treatment costs exceed one billion dollars per year [5]. Recent data revealed that thiuram rubber chemical accelerators, epoxy resin, and antimicrobials such as formaldehyde, methyldibromo glutaronitrile, and methylchloroisothiazolinone are some of the common culprits in occupational contact dermatitis [5]. Cooks, butchers, beauticians, bakers, hairdressers, and painters are primarily affected, with estimates ranging from 23.3 to 96.8 cases per 10,000 workers per year [5]. A study done at a tertiary hospital in Spain noted that the incidence of occupational contact dermatitis almost doubled in the past 7 years [6]. Workers often suffer of hand contact dermatitis, and it has been suggested by several dermatologic associations to make hand eczema and contact dermatitis a separate subtype of this condition [5].

As cosmetic product consumption is on the rise, so are the adverse reactions to these products (Fig. 1). According to a study by Zaragoza-Ninet et al., which analyzed patch test results from 1996 to 2004 and compared them to data collected from 2005 to 2013, a 5% increase in allergic contact dermatitis attributed to cosmetics was noted. Preservatives and fragrances found in soap, moisturizing cream, and hair dye are the most prominent offending agents [6]. Formaldehyde, methylisothiazolinone, and iodopropynyl butylcarbamate are the preservatives responsible for contact dermatitis [6].

Interestingly, the growing trend to practice safe sun exposure has led to sunscreen being the seventh most widely used cosmetic agent to cause allergic contact dermatitis [6]. Its main ingredient, oxybenzone, has become the most frequent

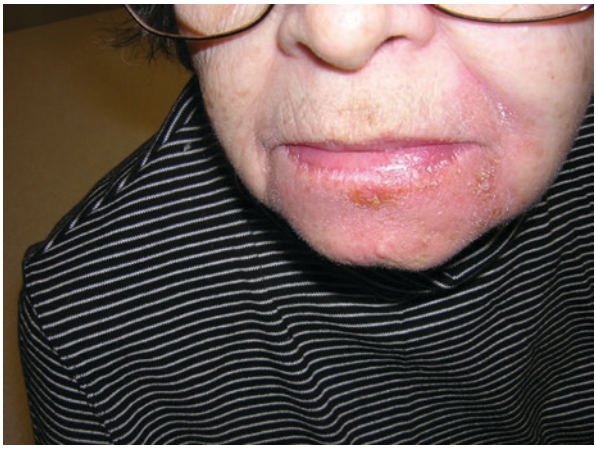

Fig. 1 Local reaction to cosmetics – James Studdiford MD/Thomas Jefferson University

Fig. 2 Poison ivy Public Domain

allergen [6]. In cosmetic-related contact dermatitis, the face, hands, and neck are the utmost affected sites [6].

Environmental allergens are very frequently the culprits of dermatitis. In particular, primary care physicians often see reactions caused by the *Toxicodendron* species: poison sumac, ivy, and oak [9]. Approximately 50–70% of population is sensitized to these species of plants [10] (Fig. 2). Urushiol found in the oleoresinous sap is the chief allergen responsible for dermatitis [10]. Direct or indirect contact can lead to manifestation of pruritus, skin desquamation, vesicles, and even bullae, typically within a 24–48-hour period [10]. Lesions appear in streak-like pattern on hands, legs, and trunk [9] (Fig. 3). This condition most commonly resolves within 1–2 weeks [10]. Typically, topical corticosteroids are usually sufficient to treat toxicodendron dermatitis. In severe cases, which may involve more than 20% of body surface area, severe itching, edema, or reaction involving the face, genitals, or hands, oral prednisone is often required [9].

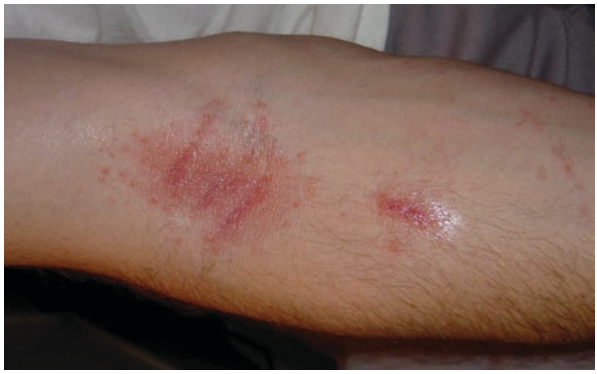

Fig. 3 Plant dermatitis by BTDenyer at English Wikipedia – Transferred from en.wikipedia to Commons, Public Domain, https://commons.wikimedia.org/w/index.php?curid=3262811

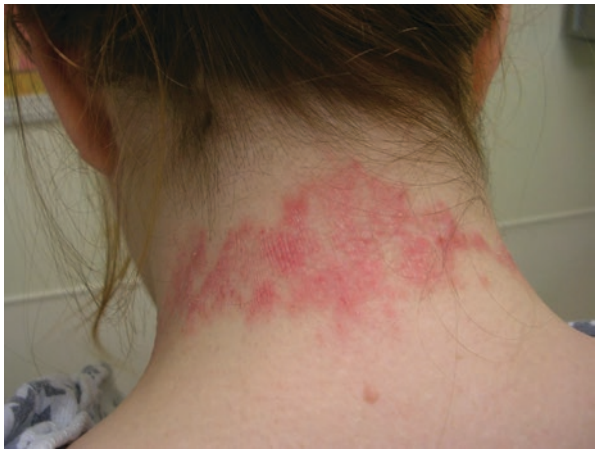

Fig. 4 Contact dermatitis from necklace – James Studdiford MD/Thomas Jefferson University

Presentation

The identification of contact dermatitis can be a difficult task due to the fact that symptoms can vary based on the causative agent and the area of the body that is affected. The hands, head, neck, legs, and feet are the sites associated with manifestation of symptoms [2]. It has been documented that ~98% of contact dermatitis cases present on the hands of patients [11]. As detailed previously, it has been shown that members of the manufacturing and healthcare professions are at the highest risk [11].

Clinical presentation of symptoms is characteristically localized to the site of contact with an agent or irritant [2] (Figs. 4 and 5). The manifestation of symptoms can occur as rapidly as within minutes or upward of hours following exposure to an insult [11]. Patients usually complain of a localized erythema with itching. Based on the agent involved in the insult, symptoms can increase in intensity. With chronic

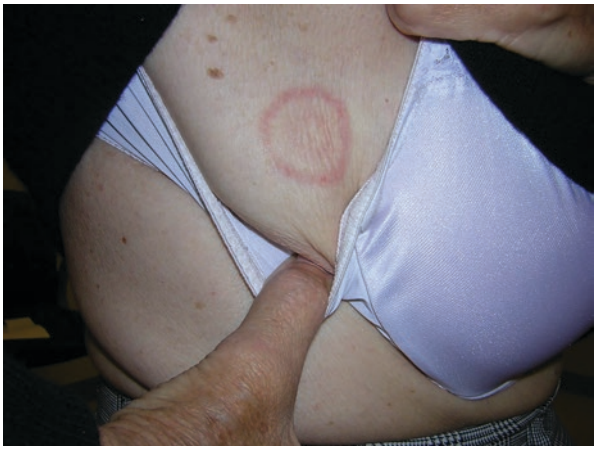

Fig. 5 Contact dermatitis metal – James Studdiford MD/ Thomas Jefferson University

contact dermatitis, the skin may present with dryness, scaling, and the development of fissures that can lead to the development of a secondary bacterial infection.

Overall, the ways that contact dermatitis presents share a great deal of similarities with a variety of other conditions. This reason makes delineation of diagnosis difficult. Thus, it is important to obtain thorough history of a patient's occupation, hobbies, cosmetic use, and family history/personal history of atopy.

Diagnosis

For many years, patch testing has been the gold standard for diagnosis of allergic contact dermatitis [12]. Irritant contact dermatitis is considered to be the diagnosis of exclusion, when patch testing is found to be negative [4]. Currently, standard panel testing consists of 35 allergens and 1 control [12]. Results of patch testing should be correlated carefully with clinical history. The process itself is very simple. Allergens are selected, based on a patient's history, then placed on patient's back, and left in place.

After 48 hours, they are removed, and the results are read immediately and then reread after 72 hours and 1 week later [12]. Reaction grading is based on its severity and is done on a scale 1+ to 3+ [4]. A certain degree of erythema should be present for a reaction to be considered positive [4]. Since anaphylactic reactions during testing have been reported, it is important to conduct this procedure in a facility with resuscitation capabilities.

Frequently standard panel testing is a good starting point, and sometimes expanded series testing is necessary, as 26% of allergens can be missed with standard allergen testing [12]. It is also possible to test with patient's own products.

Several factors should be considered when patch testing patients (Fig. 6). Individuals with recent oral corticosteroid exposure or on chronic immunosuppres-

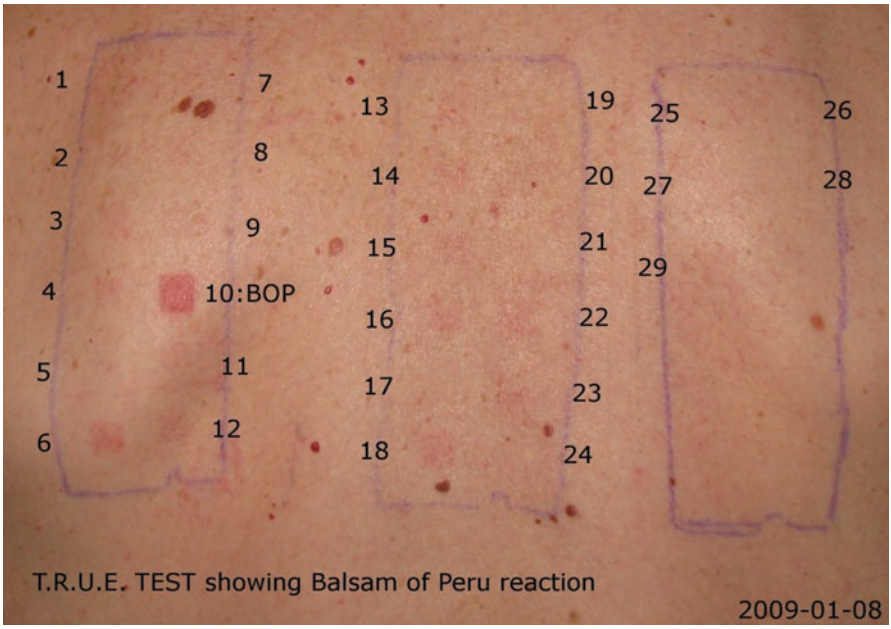

Fig. 6 Example of patch testing

sive therapy or those with recent sun exposure have a risk of having false-negative results. Patients with diffuse dermatitis can develop false-positive reactions [4]. It is also not recommended to patch test pregnant patients [4].

Frequent patient follow-up is important in interpreting patch test results. Importantly, the second reading at 72 hours can help distinguish between irritant and allergic contact dermatitis [12]. In addition, allergens that cause delayed reactions can be detected at this reading. Some of those allergens are bacitracin, corticosteroids, and disperse blue dyes [12].

Inconsistent patient follow-up, constant emergence of new allergens, and variable interpretation of test results are some of the challenges of patch testing [12]. Patch testing for fragrances and botanicals poses another challenge, as new products marketed as "natural" come on the market every day and identifying responsible allergens can be very difficult [4]. Other diagnostic testing includes repeat open application tests and lymphocyte transformation tests [4]. Repeat open application tests are useful at determining whether certain identified allergens can cause a reaction at most frequently used concentrations [4]. Lymphocyte transformation tests are easier to perform in terms of patient convenience as it only requires a blood sample [4]. However, it is limited in its availability and the number of allergens that can be tested [4].

Management

According to Lee et al., recovery time for acute contact dermatitis after exposure to a single irritant is typically 4 weeks [7]. Healing time is even longer after prolonged exposure to more than one irritant with certain studies citing numbers as high as 10 weeks [8].

Once the culprit is identified, treatment can be streamlined. Avoidance of the irritant or allergen, reduction of skin inflammation, and restoration of the epidermal barrier are all key approaches to treatment of contact dermatitis. Patient education is essential for successful outcome. It is often difficult for patients to remember the long names of allergens; thus databases such as the Contact Allergen Management Program (CAMP) and Contact Allergen Replacement Database (CARD) list products devoid of particular allergens [10, 16].

As mentioned previously, insult to skin barrier is often the first step in the pathogenesis of contact dermatitis. Thus, of foremost importance is protection and restoration of the skin barrier. Barrier protection and repair creams are often utilized. These creams enhance hydration by reducing the transepidermal water loss, thus reducing the effect of irritants on the protective barrier [14]. Although it is very difficult to standardize.

studies, some researchers have found that barrier creams can be protective against four of the irritants such as sodium laureth sulfate (SLS), sodium hydroxide (NaOH), lactic acid, and toluene [15]. Barrier creams can contain a variety of combinations of ceramide.

and petrolatum, one of the oldest barriers known. Ceramide, hyaluronic acid, and palmitoylethanolamide have been found helpful in skin hydration maintenance [15].

In addition to cold compresses or calamine lotion, topical corticosteroids can often be effective in the acute phase of allergic contact dermatitis. Several factors such as location, expected duration of treatment, and previous corticosteroid use affect choice of topical treatment. Steroids are classified into five groups based on their structure: triamcinolone acetonide, hydrocortisone type, betamethasone type including betamethasone dipropionate type, and methylprednisolone acetonate [13]. Typically, low-potency corticosteroids should be used in areas where the skin is thinner, such as the face or genital area [13]. High-potency topical corticosteroid can be used for reactions that are localized. Moderate-potency preparations can be used for more widespread reactions [10]. Patients should be advised to apply the minimum amount of medication to the affected area as well as to not exceed the prescribed treatment duration.

Severe reactions can often require oral steroid treatment. Prednisone tapered over 2–3 weeks has been shown to be more effective in decreasing the risk of rebound reactions as well as use of other medications [9].

Prevention

In terms of prevention of contact dermatitis, discontinuation of the irritating agent is the best measure to alleviate reoccurrence. If avoidance of the agent is impossible, then the addition of a barrier can aid in preventing contact dermatitis. Masks, protective eyewear, and gloves are excellent sources for creating a barrier [16].

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Acne Vulgaris

Christine Marriott and Neil S. Skolnik

Acne vulgaris (AV) is one of the most common skin conditions treated in a primary care setting. Acne can occur in all age groups but affects 85% of adolescents with 15–20% of adolescents experiencing moderate to severe acne. Acne can frequently persist into adulthood, and there is a prevalence of about 12% in adult women. While there is no mortality, there can be significant physical and psychological effects for patients, including scarring, poor self-image, depression, and anxiety [1, 2].

Pathophysiology

Acne is a multifactorial process that affects the pilosebaceous units of the skin. It often begins in early puberty with increased sebum production and mid-facial comedones, which are then followed by inflammatory lesions. There are four processes that contribute to acne formation: increased sebum production, the release of inflammatory mediators in the skin, alteration of the keratinization process leading to comedones, and colonization of the follicles with *Propionibacterium acnes* [3].

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Clinical Characteristics

Acne is characterized by open and closed comedones (Fig. 1), as well as inflammatory lesions (Fig. 2), such as papules, pustules, and nodules. Lesions typically occur on the face, neck, chest, and back due to the higher concentration of sebaceous glands in these areas. Other conditions that may present with a similar appearance to acne include bacterial folliculitis, hidradenitis suppurativa, miliaria, perioral dermatitis, pseudofolliculitis barbae, rosacea, and seborrheic dermatitis [4]. There are several grading systems for assessing acne severity, but there is neither a gold standard nor a standardized system that is consistently used in practice. The current

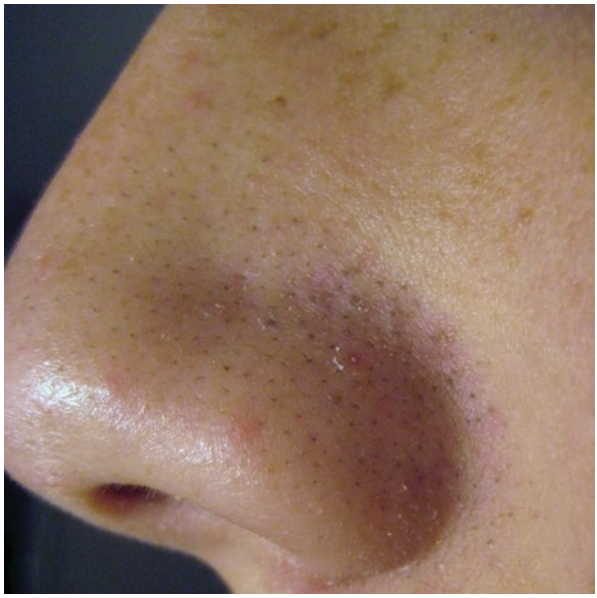

Fig. 1 Comedonal acne. (By Elecbullet, own work, public domain, https://commons.wikimedia.org/w/index.php?curid=6921982)

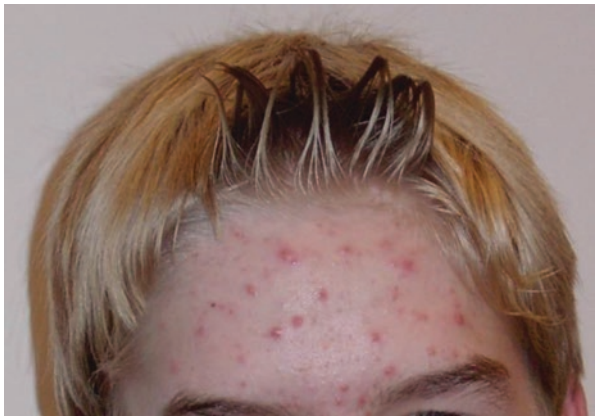

Fig. 2 Inflammatory acne. (Wikicommons: public domain)

acne grading systems involve several factors, including lesion size, density, and type, as well as distribution and intensity on affected anatomical sites [5]. Clinical assessment of acne severity should determine the initial treatment approach.

Treatment

Recommended Approach

Treatment of mild acne is primarily topical and should begin with either benzoyl peroxide (BP) or a topical retinoid (TR). Another option for mild acne is to start with topical combination therapy. Topical combination therapy can include the following: BP plus a topical antibiotic; TR + BP; or TR + BP + topical antibiotic. Combination therapy can be given either with separate application of the different medicines or by using fixed combination products that include the separate components in one formulation. Alternative treatments for mild acne that is not improving include topical dapsone, switching retinoid medications, or adding another topical agent.

Moderate acne can be treated with either topical combination therapy as described above, or systemic antibiotics plus a TR + BP, with or without the addition of a topical antibiotic as well. Female patients may also consider combined oral contraceptives or spironolactone for the treatment of moderate acne. If the treatment is not effective, one can consider changing the topical combination therapy or changing the oral antibiotic. Oral isotretinoin can also be considered as an alternative treatment in some cases of moderate acne.

For severe acne, oral isotretinoin or oral antibiotics with topical combination therapy are considered first-line options, with the addition where appropriate of COCs or oral spironolactone.

One can also consider changing the oral antibiotic in patients who are not responding to treatment.

Medications

Topical Therapies

There are several topical agents for the treatment of acne vulgaris, which are available over the counter and by prescription. The choice of topical therapy and number of agents may be influenced by several factors, including the patient's age, affected site, extent and severity of disease, and the patient's preferences regarding treatment. Topical agents can be used alone, in combination with other topical agents, or in combination with oral agents. The most commonly used topical therapies are benzoyl peroxide, antibiotics, retinoids, azelaic acid, sulfone agents, and salicylic

acid. All of the topical therapies have an A recommendation, based upon level I or II evidence except for salicylic acid, which has a B recommendation with level II evidence.

Benzoyl peroxide is an antibacterial agent, which is recommended as a first-line treatment for mild acne and is often used in combination with other therapies for all types of acne vulgaris. The mechanism of action involves killing *P. acnes* through the release of free radicals, and it is mildly comedolytic. There is no bacterial resistance to this agent. Because of this property, benzoyl peroxide is often added to topical antibiotic therapy to increase effectiveness and reduce the development of resistance. Benzoyl peroxide is available in strengths from 2.5% to 10% and in a variety of formulations including washes, foams, creams, and gels, which can be used as leave-on or wash-off agents. Although there are a variety of strengths of BP, it is not clear that increased strength leads to increased efficacy. Side effects include dose-dependent skin irritation, bleaching of fabric, and uncommonly contact allergy. Results can be seen in as few as 5 days but may often take 6–8 weeks. Maximum response is seen at 8–12 weeks of use.

Topical antibiotics, including clindamycin and erythromycin, can also be used in the treatment of AV. They accumulate in the follicle and work through both antiinflammatory and antibacterial effects. Topical antibiotics should be used in combination with benzoyl peroxide because of increased efficacy and decreased development of resistance. The preferred topical antibiotic is clindamycin 1% solution or gel. Topical erythromycin 2% is available in cream, gel, lotion, or pledget formulations but is less effective than clindamycin due to increased resistance. Both antibiotics are available in fixed-dose combinations with benzoyl peroxide, which may enhance compliance with the treatment regimen. There are rare reports of diarrhea and *Clostridium difficile* colitis with topical clindamycin use, but the risk of these side effects appears to be low.

Topical retinoids are vitamin A derivatives that are a mainstay in the treatment of acne vulgaris. They are comedolytic and antiinflammatory and work to resolve the precursor microcomedonal lesion. Retinoids are recommended for the treatment for comedonal acne and, when used in combination with other topical agents, as an effective treatment for all types of acne. They can also be used for maintenance of clearance after completing a course of oral therapy. There are currently three active agents available: tretinoin (0.025–0.1% in cream, gel, or microsphere gel vehicles), adapalene (0.1% and 0.3% gel or 0.1% lotion), and tazarotene (0.05% and 0.1% cream, gel, or foam). Because the retinoids each bind to different retinoic acid receptors, there are slight differences in efficacy and tolerability. There are also combination products available: adapalene 0.1%/BP 2.5%, adapalene 0.3%/BP 2.5%, and clindamycin phosphate 1.2%/tretinoin 0.025% gel. The main side effects of retinoids include dryness, peeling, erythema, and skin irritation. The side effects are generally dose dependent. Acne may worsen in the short term after a topical retinoid is started. While higher concentrations may be more effective, reducing the potency or frequency of application may be helpful for patient who are experiencing these side effects. Tretinoin may be oxidized and inactivated by BP, so these agents should be applied at different times of day. Similarly, some formulations of tretinoin

are not photostable and should be applied at bedtime. Adapalene, tazarotene, and tretinoin microsphere formulation do not have these restrictions. However, topical retinoids do increase the risk of photosensitivity, so patients should be counseled on daily sunscreen use. Another important consideration about retinoid use is they are not recommended in pregnancy. Tretinoin and adapalene are category C, and tazarotene is category X, so patients should be counseled on these pregnancy risks when discussing retinoid use.

Azelaic acid 20% is another topical agent, which may be useful in patients with sensitive skin. It is mildly effective as a comedolytic, antibacterial, and antiinflammatory agent. The agent does have a mild lightening effect, so it can be used in patients with dyspigmentation. Azelaic acid is category B in pregnancy.

Dapsone, which is a sulfone agent, is available in a 5% gel BID and a 7.5% gel once daily for the treatment of acne vulgaris. The mechanism of action is poorly understood, but it is thought to work as an antiinflammatory agent. Topical dapsone is primarily effective in reducing inflammatory lesions and seems to be more beneficial for female patients, as opposed to males and adolescents. Dapsone can be combined with topical retinoids if comedonal lesions are present. Dapsone may be oxidized if applied with BP, which causes orange-brown discoloration. Topical dapsone 5% gel and 7.5% gel is pregnancy category C.

Salicylic acid is a comedolytic agent for the treatment of acne vulgaris. It is available over the counter in 0.5–2.0% strengths and both wash-off and leave-on preparations. Salicylic acid is generally well tolerated, but clinical trials demonstrating its efficacy are limited.

Oral Treatment

Systemic antibiotics have been used in the treatment of acne vulgaris for many years, and they are indicated for use in moderate to severe inflammatory acne. They should always be used in combination with topical therapies, specifically a retinoid or BP. Generally, systemic antibiotics should be used for the shortest possible duration, often 3 months, to prevent the development of bacterial resistance. Topical therapies should be continued after the completion of systemic antibiotic therapy for maintenance of clearance. Tetracyclines and macrolides have the strongest evidence for their efficacy in acne vulgaris. Other antibiotics that can be used are trimethoprim/sulfamethoxazole (TMP/SMX), trimethoprim, amoxicillin, and cephalexin. However, their evidence is limited, so they should only be used in patients who cannot tolerate tetracyclines or macrolides. The tetracycline class can cause photosensitivity. This effect is much more with tetracycline and doxycycline than minocycline.

The tetracycline class of antibiotics is considered first-line therapy for moderate to severe acne, except when contraindicated. The class also has antiinflammatory effects. Doxycycline and minocycline are considered equally effective but more effective than tetracycline. There are limited studies comparing dosing of tetracyclines. Minocycline should be dosed in an extended release form at 1 mg/kg, and

doxycycline should be dose at 1.7–2.4 mg/kg. There is also evidence of efficacy of doxycycline at subantimicrobial doses (20 twice daily to 40 mg daily). These antibiotics are contraindicated in pregnancy or children under 8 years of age.

Macrolide antibiotics, erythromycin and azithromycin, can be used in the treatment of moderate to severe acne. There is also an antiinflammatory component to their action. Azithromycin has been studied in open-label studies with a variety of pulse-dose regimens ranging from three times per week to 4 days per month for 2–3 months. Macrolides are a good alternative systemic antibiotic for patients who are not candidates for tetracyclines.

TMP/SMX and trimethoprim have also been used as systemic antibiotics in the treatment of acne vulgaris. There is one small double blind trial showing that TMP/SMX is as effective as oxytetracycline, but the data is limited.

Penicillins and cephalosporins can also be used in the treatment of acne, but they should be reserved for circumstances when other antibiotics cannot be used, such as pregnancy or medication allergies, because their data is limited. They work by binding to the penicillin-binding proteins in the bacterial cell membrane and inhibit wall synthesis.

Combined oral contraceptive pills (COCs) are another option for the treatment of acne in female patients. There are currently four COCs that are approved by the FDA for the treatment of acne in women who also desire contraception: ethinyl estradiol/norgestimate (Ortho Tri-Cyclen), ethinyl estradiol/norethindrone acetate/ferrous fumarate (Estrostep Fe), ethinyl estradiol/drospirenone (YAZ), and ethinyl estradiol/drospirenone/levomefolate (Beyaz). The pills work by decreasing androgen production in the ovary and increasing sex hormone-binding globulin, which binds free testosterone and prevents it from binding to the androgen receptor. They also decrease 5-alpha-reductase activity and block the androgen receptor.

There have been numerous randomized controlled clinical trials that have demonstrated the efficacy of COCs in reducing both inflammatory and comedonal lesions. A 2012 Cochrane meta-analysis included 31 trials totaling 12,579 women in assessing the effect of COCs on acne. There were nine trials which compared a COC to placebo, and all of the COCs were effective in reducing acne. Seventeen trials compared two COCs, but there were no consistent differences in efficacy between formulations and dosages. Overall, there is strong evidence for the efficacy of COCs, but there is not consistent evidence for the superiority of a particular COC [6].

Some women may present with symptoms of hormonally induced acne, such as flares related to their period or hirsutism. While most patients with acne will have normal hormonal levels, patients with both acne and signs of hyperandrogenism should be evaluated with endocrinologic testing. Treatment with COCs is not limited to patients with signs and symptoms of hormonally induced acne. They are effective for acne treatment in women with and without these symptoms. Improvement of acne with COCs generally takes a few months. Randomized clinical trials show a significant improvement in acne by the end of the third cycle. Patients should be counseled accordingly, and COCs may also be combined with other acne medications at the onset of treatment.

While COCs are a good treatment option for many female patients with acne, there are significant risks that need to be considered. FDA approval of all COCs for acne specifies that they are approved for treating acne in women who also desire contraception, not acne alone. While COCs increase the risk of several serious adverse events, the overall risk in women of reproductive age is low. Caution should be used in patients with other comorbidities that increase their risk of adverse events.

Spironolactone is an aldosterone receptor antagonist that has antiandrogen properties. While it is often used off label, it is not FDA approved for the treatment of acne. Spironolactone decreases testosterone production and competitively inhibits binding of testosterone to androgen receptors in the skin. There have been two small, prospective, placebo-controlled studies which showed significant improvement in acne severity and sebum productive at doses from 50 to 200 mg daily, as well as a retrospective study, which found 66% of female patients were clear or significantly improved at doses of 50–100 mg daily. However, a Japanese study of both male and female patients was discontinued due to the development of gynecomastia in male patients while showing clinical improvement in the female patients [7]. Due to small number and size of trials, a Cochrane review concluded that there was insufficient evidence to support the use of spironolactone in acne. Nonetheless, the American Academy of Dermatology guidelines support the use of spironolactone for acne in select women based on the available evidence and expert opinion.

Oral prednisone dosed at 5–15 mg daily has been shown to be effective in the treatment of acne. However, the long-term side effects of corticosteroids prevent routine use for the treatment of acne. Prednisone dosed at 0.5–1 mg/kg/day is used for the treatment of acne fulminans and the prevention of isotretinoin-induced acne fulminans-like eruptions. Oral steroids should be tapered gradually while starting isotretinoin or oral antibiotics to reduce the risk of relapse.

Oral isotretinoin is approved by the FDA for the treatment of severe recalcitrant acne (Fig. 3). It has been used for 35 years and has proven successful for most patients with severe acne. Isotretinoin causes decreased sebum production, acne lesions, and scarring. It can also be considered in the treatment of moderate acne that is resistant to other treatments, relapses quickly after the discontinuation of oral antibiotics, or produces significant scarring or psychosocial distress.

For severe acne, isotretinoin is commonly dosed at 0.5 mg/kg/day for the first month, and then increased to 1.0 mg/kg/day for the next month, as tolerated. Doses generally range from 0.1 mg/kg/day to 1.0 mg/kg/day. There is some efficacy regardless of dose, but the decrease in sebum production is dose dependent, and there is a lower rate of relapse with higher dosing. However, the dose-dependent benefit seems to plateau beyond a cumulative dose of 150 mg/kg. In treatment-resistant or quick-relapsing moderate acne, lower doses of 0.25–0.4 mg/kg/day have been found to be equally effective to conventional dosing and are not associated with higher relapse rates. Intermittent dosing regimens are not effective for isotretinoin. Since isotretinoin is lipophilic, it should be taken with meals.

Common side effects of isotretinoin involve the mucocutaneous, musculoskeletal, and ophthalmic systems and mimic the symptoms of hypervitaminosis A. Serum cholesterol, triglycerides, and transaminases can rise during treatment and should

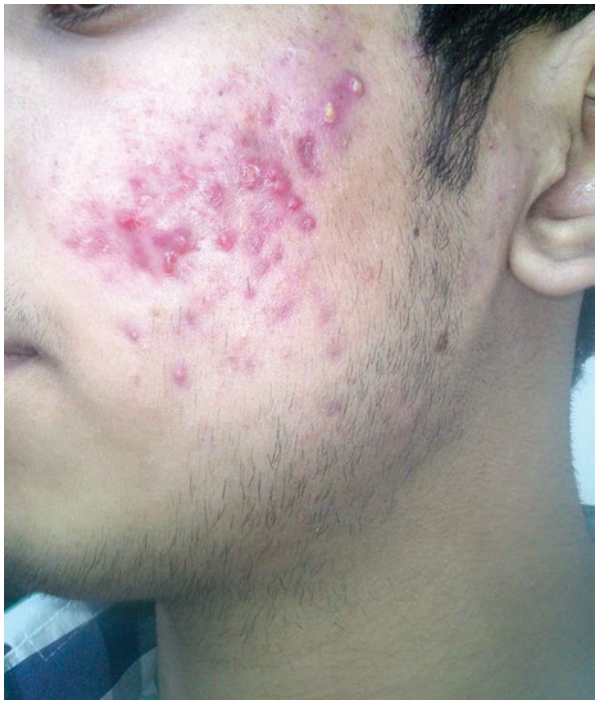

Fig. 3 Cystic acne. (By User:Naveenhooda23 – own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=30253958)

be monitored. There is concern about a possible relationship between oral isotretinoin use and inflammatory bowel disease, but more evidence is needed. There have also been reports of mood changes, including depression and suicidal ideation in patients taking isotretinoin. While there have been several studies that found no link between isotretinoin and depression on a population level, physicians should monitor their patients for these symptoms.

Because of the risk of teratogenic effects, the FDA has mandated that all patients receiving isotretinoin must participate in the iPLEDGE risk management program, which requires abstinence or two forms of birth control. Female patients of childbearing age should be counseled about contraceptive options, and long-acting reversible contraceptives should be offered when appropriate. While isotretinoin requires monitoring and carries the possibility of significant side effects, it is an effective treatment option for patients with severe recalcitrant acne.

Physical Modalities

There is limited evidence for the use of physical modalities for the treatment of acne. While several light and laser devices have been investigated, there is the most evidence for photodynamic therapy (PDT). During PDT treatments, a photosensitizer

is applied to the skin and absorbed into the pilosebaceous units. A laser or light then activates the photosensitizer, which creates singlet oxygen species that damage the sebaceous glands. While this treatment is promising, additional studies are needed. Chemical peels using glycolic or salicylic acid have also been shown to mildly improve comedonal acne. However, the results are transient, and multiple treatments are needed. Intralesional injections of triamcinolone acetonide are often used for the management of large nodular lesions. While there is rapid improvement of the lesion, there are concerns about local atrophy, systemic absorption of the steroid, and adrenal suppression. These risks should be minimized by reducing the concentration and volume of steroid used. While there is limited evidence for comedo removal, it is a routinely used technique and may be helpful for resistant lesions.

Alternative Therapies

Several herbal and alternative therapies have been used for the treatment of acne, but their evidence is limited. There are two clinical trials that demonstrated that topical tea tree oil is effective. One showed it was comparable to BP, but better tolerated. Other herbal agents that have been used are topical and oral ayurvedic compounds, oral barberry extract, and gluconolactone solution. There is weak evidence for the benefit of biofeedback. Although most of these treatments are well tolerated, there is limited evidence about their safety and efficacy.

Diet

Patients may ask about the role diet plays in their acne. There is some data that suggests that high glycemic diets are associated with acne. There were two recent randomized studies that found significant improvement in acne severity with a low glycemic diet, but the studies were limited by small sample sizes. There have also been several observational studies that suggest that the risk of acne is increased with milk consumption, especially skim milk.

Conclusion

In conclusion, acne is a common skin condition encountered in primary care. There are several treatment options, and the intensity of treatment should be guided by clinical severity. Mild acne should be treated with benzoyl peroxide, retinoids, or a combination of topical treatments. Systemic antibiotics should be combined with topical therapies for moderate to severe acne. Female patients may

also consider using combined oral contraceptives and spironolactone. Oral isotretinoin is an effective option for severe acne but requires close monitoring and contraceptive counseling.

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Cutaneous Warts

R. Drew Durtschi and John J. Russell

Introduction

Human papillomavirus (HPV) is a dsDNA virus that infects epithelial skin layers and mucous membranes. Over 150 serotypes of HPV have been identified [3]. While certain serotypes have a predisposition for specific areas of the body, it is impossible to ascribe a serotype solely on location. Also, knowing the serotype does necessarily affect the treatment.

The size, shape, and timeline of HPV infections are variable [1]. However, the basic lesion is classically identified pathologically as hyperkeratosis of the stratum corneum, with thickening of the stratum spinosum and stratum granulosum. There is also characteristic elongation of the rete ridge and blood vessels at the dermoepidermal junction that are seen as black or red spots on both visual examination and dermatoscope [2].

The growths are called verrucae or more commonly "warts." Warts can appear alone or in groups. When a group of warts grow together, it can be referred to as a plaque.

Cutaneous warts are generally described in six categories:

- Common warts (verruca vulgaris)
- Plantar warts (verruca plantaris)
- Flat or plane warts (verruca plana)

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- Intermediate warts (combined common and flat)
- Mosaic warts (or plaque)
- Periungual warts (under or around the nail bed)

An additional special classification can sometimes be given to filiform warts, which have long stalks and are often seen on the face.

Epidemiology

Cutaneous warts are very common among children and young adults [1]. They are also seen more commonly in professions that handle fish, poultry, or other meat [4]. Infection occurs with direct skin contact to the human papilloma virus. A typical incubation period is variable from 2 to 6 months [1].

The HPV can reside on the skin of healthy individuals for long periods of time. Once the infection begins to erupt, warts can be seen spreading in a linear fashion as a result of the Koebner phenomenon of self-scratching and auto-inoculation [5].

One observational study showed half of cutaneous warts resolved within 1 year and two-thirds within 2 years; however, it is not uncommon for warts to persist for several years [1]. However, treatment may be desired if there is discomfort or cosmetic concern or in immunocompromised patients who can develop resistant lesions. The end point of all treatment is resolution of the wart. This is often best appreciated by return of normal lines and texture. Recurrence of warts is common in all age groups.

Diagnosis

Benign cutaneous warts are diagnosed based on clinical appearance (Figs. 1, 2, 3, and 4). A dermatoscope can be useful in identifying key features such as densely packed papillae in a well-defined region which disrupts normal skin lines. Also, small homogenous red or black dots from thrombosed capillaries are commonly

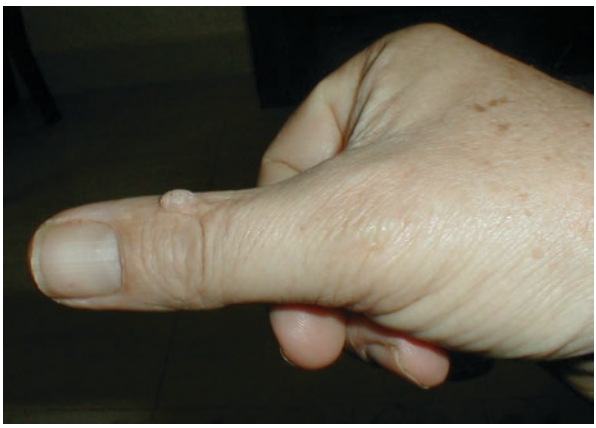

Fig. 1 Verruca vulgaris. (By Lucien Mahin – own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=15168704)

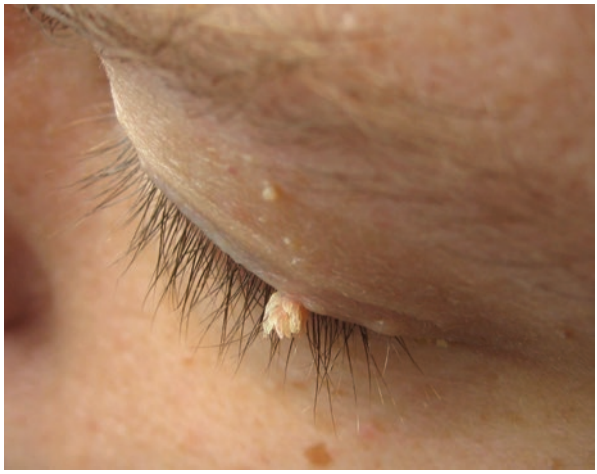

Fig. 2 Wart on eyelid. (By Marionettem.richter67@yahoo.de; own work by uploader (m.richter67yahoo.de), CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=6087673)

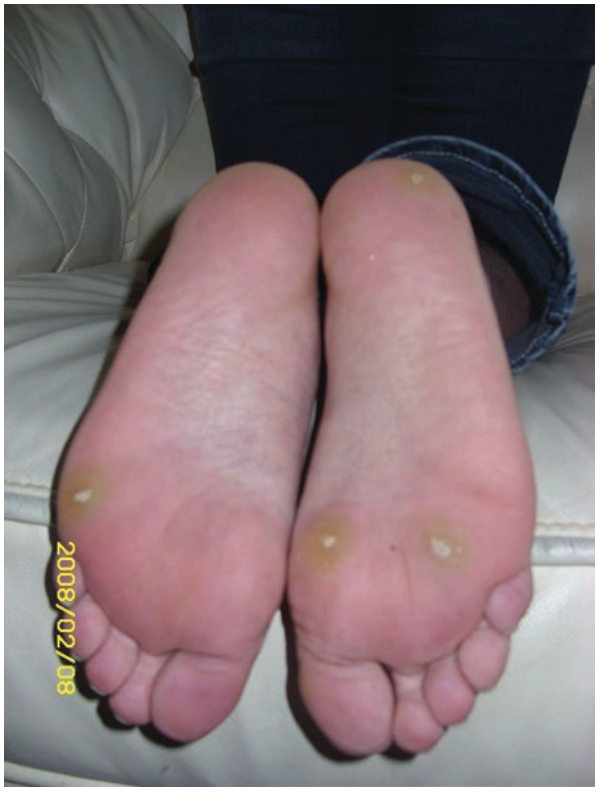

Fig. 3 Plantar wart. (By Schweintechnik - own work, public domain, https://commons.wikimedia.org/w/index.php?curid=3383897)

seen within the circumscribe area. The color of the lesion itself can vary from brown to yellow to white depending on vascularity, age, or patient manipulation of the site.

If diagnosis is unclear, a small blade can be used to shave the area of hyperkeratosis to try and reveal the small red/black spots at the base of the lesion. A shave biopsy is generally not required for diagnosis [1].

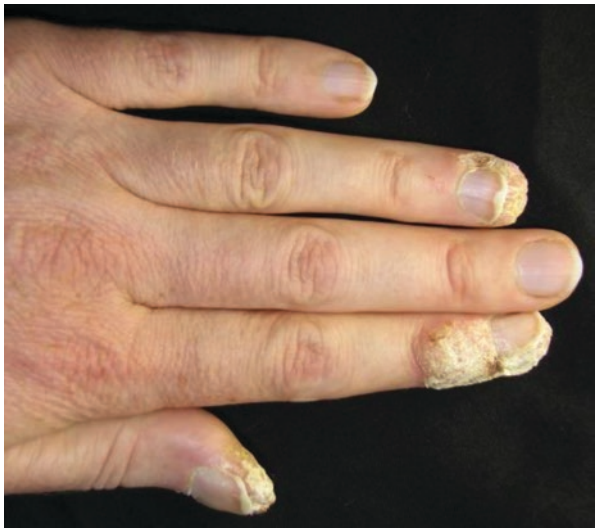

Fig. 4 Periungual warts. (DermNet NZ)

Management

The most important aspect in the management of warts is to discuss with patients the risks and benefits of treatment. Most warts will resolve spontaneously, and even with treatment, the time to resolution can be difficult to assess. Again, resolution of the wart does not necessarily mean elimination of the HPV virus from the host. It should also be explained that there is possibility for warts to erupt in other locations. With this understanding, the next step is to decide the best treatment procedure for the patient.

When creating a treatment plan, consideration should be given to proper classification of the wart. Other important factors are location, size, and ability of patient to follow the instruction of the therapy.

Treatment

Many methodologies have arisen for the treatment of cutaneous warts, some with very limited data [6]. Given the natural coarse and self-limiting nature of HPV cutaneous infections, study results can be difficult to interpret. Therefore, wisdom will be paramount when selecting a treatment modality for your patient.

Salicylic Acid

Salicylic acid is a keratolytic agent that slowly eats away at the HPV-infected skin layers. It may also initiate an immune response due to its irritating nature [1]. It is available over the counter. No clinical study has identified a superior concentration, but 17% is the most common form [6].

Salicylic acid is available as a liquid or a gel and impregnated on a bandage. It is affordable and generally safe with the major side effect being irritation to the skin surrounding the wart [1]. A random trial showed a 73% cure rate within 6–12 weeks, as compared with only 48% in the placebo group [6]. Seventeen percent salicylic acid should not be used on the face, as it can cause changes to pigmentation [1].

As with all treatment options, it is important to discuss the proper application and length of treatment with patients to ensure optimal results. Begin by soaking the wart area with warm water for 5 minutes, and gently file down the rough area. Apply the salicylic acid directly to the wart carefully to avoid damaging the surrounding tissue. Repeat this process daily (or every other day if using a salicylic imbedded patch) until the wart has cleared. If the wart persists longer than 3 months, the lesion should be re-evaluated [7].

Cryotherapy

Liquid nitrogen (LN2) is a common treatment found in most primary care offices, but there are also fluorocarbon products for freezing that are sold as over-the-counter products. They are generally more expensive than the salicylic acid. Liquid nitrogen works by freezing and killing the infected skin, thus allowing the body to create a healthy new area [1].

LN2 is applied by first removing the dead skin on top of the wart with a scalpel. Next apply the LN2 for about 10–30 seconds (or until a white frozen area appears approximately 2 mm around the area). It is acceptable, although not required, to use a second application. This can be particularly helpful when treating plantar warts. When using the freeze-thaw-freeze method, wait until the white frozen area has cleared, and then a second application of LN2 can be administered. Overexposure to LN2 during application can result in increased pain and blistering, so attention must be given to keep the area of application focused [7].

HPV is very contagious and has been shown to survive in liquid nitrogen; therefore, any equipment used for application and treatment of warts should be discarded [1].

Treatment can be repeated every 2–3 weeks until the wart has been cleared. Usually, resolution occurs within 3 months. If the lesion persists, despite adequate treatment, biopsy should be considered. No evidence has demonstrated that more frequent treatments result in a faster resolution. In fact, decreased time between treatments can increase pain without affecting the wart [6].

When compared with salicylic acid, studies show limited difference in effectiveness, although compliance with the less frequent applications of LN2 seems to be easier for the majority of patients [6]. Disappearance of the wart occurred 50–70% of the time after three to four treatments.

As mentioned previously, the most common adverse effect of cryotherapy was pain and blistering. Occasionally, changes in skin pigmentation (especially in those with dark skin) can occur. Onychodystrophy can be seen following aggressive treatment of periungual warts [8]. While rare, damage to nerves or tendons can occur if application occurs beyond the border of the wart or if the LN2 is applied for excessive amounts of time.

Candida and Mumps Skin Antigens

Common antigens such as *Candida* and mumps have been shown to cause local, cell-mediated HPV-specific responses that can target a specific wart and, in turn, signal an immune response at other sites. One study showed that in patients with recalcitrant warts, injection of a skin antigen resulted in 60% cure rates when compared to the placebo group [6]. When considering this method, it is important to consider the immunocompetency of the patient, since it relies on a T cell response to remove the wart.

Antigen injections are a common practice, and the antigens are easily available at most medical supply companies. However, this treatment modality is rarely used in the primary care setting.

The most frequent complaints are pruritus, burning, and pain at the injection sites. In one study, there were also two cases of discoloration to the distal digits that occurred after injection of the *Candida* skin antigen to a subungual wart. Both cases resolved without further complication.

Others

Many other treatment modalities have been discussed with limited effectiveness. Duct tape is often mentioned as a possible home remedy; however, two recent studies showed no effectiveness when compared to placebo [6]. Therefore, duct tape can be considered as an adjunct to salicylic acid, but there is insufficient evidence to establish its role as a monotherapy.

Intralesional bleomycin has also been studied in the treatment of warts. It is a chemotherapeutic agent that inhibits DNA synthesis and causes tissue necrosis that can stimulate an immune response. However, studies have shown inconsistent results. Since treatment with bleomycin can result in significant systemic drug exposure, it should be avoided in the treatment of children, pregnant women, or patients with compromised vascular health. It can result in pain, swelling, pigment changes, and necrosis. Bleomycin is rarely used in the primary care setting [6].

Systemic treatments have been proposed as possible treatment for cutaneous warts. Studies have looked at things such as cimetidine, zinc, and homeopathic treatments. Although there are some anecdotal studies, there is a paucity of randomized double-blinded trials that show much evidence of efficacy [9].

Surgical removal via curettage has also been shown to have success rates between 65 and 85%. Complications can include scarring, which can be problematic, especially on the feet and hands. Recurrence also seems to be an issue with manipulation. No controlled studies have been performed to compare curettage to placebo, but it is likely to be effective when performed by a competent provider [1].

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Herpes Infections: Cutaneous Manifestations

Lionel S. McIntosh

The *Herpesviridae* family is a large group of DNA viruses that are ubiquitous across many animal species. Herpesviruses cause lytic and latent life-long infections in animal and human hosts. The virus family name herpes – a derivative of the Greek word "herpein," which means to creep – reflects this recurring pattern of infectivity and latency in the host [1].

There are nine herpesvirus species – human herpesviruses (HHV) – that cause infection in human hosts. These viruses are HSV 1 (HHV 1), HSV 2 (HHV 2), varicella zoster (HHV 3), Epstein-Barr virus (HHV 4), human cytomegalovirus (HHV 5), human herpesvirus 6 (HHV 6A and 6B), human herpesvirus 7 (HHV 7), and Kaposi sarcoma-associated herpesvirus (HHV 8) [2]. Cutaneous manifestations are central to many herpes infections and will be highlighted in this overview. HHV 5 has non-specific cutaneous findings and will not be addressed in this discussion.

Herpes Simplex Viruses (HSV 1 and 2)

HSV 1 and HSV 2 are classified as herpes simplex viruses. Both viruses are ubiquitous with estimates of approximately 90% of the global population being exposed to HSV 1 and 15–80% exposed to HSV 2 [3–5]. The distinction between the two viruses has traditionally been based on the anatomic locations where each preferentially causes infections. HSV 1 primarily causes infection of the oral mucosa and face, whereas HSV 2 is the causative agent in anogenital infections. Notwithstanding

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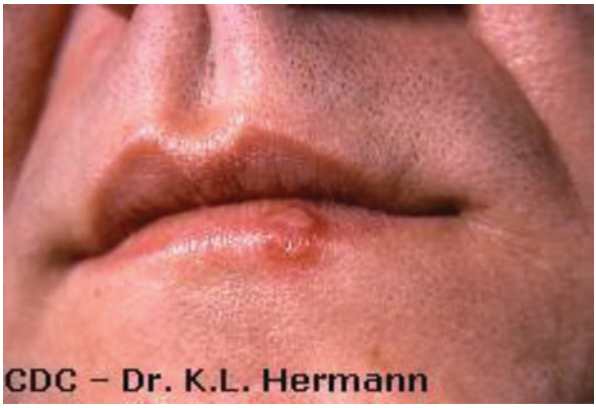

Fig. 1 Herpes labialis (CDC)

infection patterns, HSV 1 has been isolated as the virion in anogenital herpes infections, and HSV 2 has been isolated in orofacial herpes outbreaks [6].

Herpes simplex 1 (HSV 1) is colloquially known as a "cold sore" (Fig. 1), and inoculation occurs by droplet infection requiring direct contact of the virion with a mucosal or an excoriated skin surface. Infection usually occurs by kissing, direct contact with vesicles or blisters, and infected fomites. The characteristic features of HSV 1 infection are multiple clustered, small, clear, fluid-filled vesicles overlying an inflamed erythematous base on the lip or skin of the face [7]. The affected area can be painful and is accompanied by tingling and stinging sensations. A viral prodrome of fever, malaise, and localized lymphadenopathy can accompany outbreaks which are self-limiting and last for approximately 10–14 days [8].

Herpetic gingivostomatitis and pharyngitis are often seen during a primary HSV 1 infection. Symptoms include erythematous gums that bleed easily with multiple painful, small white/yellow-gray, fluid-filled vesicles on the gingiva, tongue, palate, and buccal surfaces. The initial outbreak is usually accompanied by a prodrome consisting of mouth pain, pharyngeal edema, cervical lymphadenopathy, tonsillar exudate, anorexia, and myalgias [7].

Herpes simplex virus 2 (HSV 2) infections (genital herpes) predominate in the sexually active segment of the population. It is transmitted through sexual contact and is transmitted as the virus particles actively shed and increase the risk of infection. The virus, once transmitted, has an incubation period of between 4 and 7 days in the host [9]. A viral prodrome of itching, burning, inguinal lymphadenopathy, and erythema heralds the eruption of small, clear/skin-colored vesicles with an erythematous base in clusters on the glans or shaft of the penis, foreskin, scrotum, vulva, vagina, cervix, clitoris, perineum, pubis, buttock, inner thigh, and anus [10] (Fig. 2). Once erupted, the vesicles crust and ulcerate in 7–10 days and heal in 14–21 days.

In mild, uncomplicated cases of orolabial herpes, no treatment is required. The vesicles blister, ulcerate, and heal over the course of the active infection. Topical antiviral preparations of acyclovir and penciclovir have not been shown to accelerate healing or significantly reduce symptoms of an active infection [11].

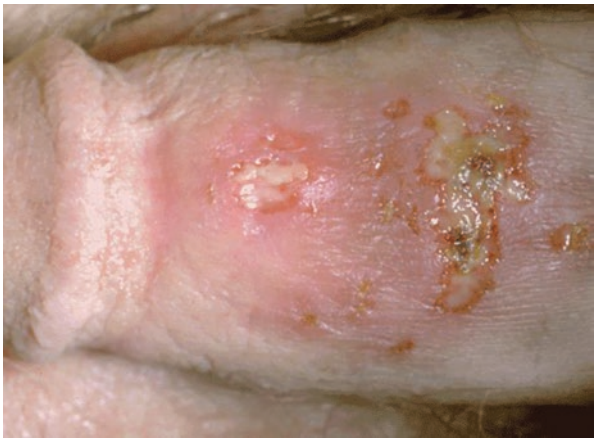

Fig. 2 Herpes of the penis. (By Unknown; http://www.umedik.ru/2011/genitalnyj-gerpes/,CC0, https://commons.wikimedia.org/w/index.php?curid=12666289)

Genital herpes infections treated with oral antiviral preparations have been shown to decrease pain, accelerate crusting of vesicles, and complete resolution of outbreak. Oral acyclovir 400 mg three times daily for 7–10 days has been shown to be an effective treatment regimen for primary outbreaks. Recurrent herpes infections can be treated with acyclovir 400 mg administered five times daily for 5 days. Oral acyclovir 400 mg twice daily is the suggested pharmacological approach for chronic suppression therapy of HSV 2 infections. Famciclovir 250 mg three times daily for 7–10 days and valacyclovir 1 g twice daily for 7–10 days are also approved treatments for primary genital herpes outbreaks [9].

Varicella Zoster (HHV 3)

Varicella zoster virus causes the highly contagious exanthem called chicken pox. Chicken pox predominates in the pediatric population and has a mild, self-limiting course that resolves anywhere from 2 to 4 weeks. Infected individuals are contagious for a period of 1–2 weeks despite persistence of the rash beyond this time course [12]. In the United States, approximately 90% of adults obtained immunity through infection with the virus. Since the introduction of the varicella vaccine in 1995, 90% of children have been vaccinated against the virus [13].

Chicken pox is an airborne infection and is easily transmitted via cough or sneeze of an infected host or direct contact with open blisters [14]. The varicella virus usually infects its host 1–2 days before the appearance of the characteristic rash of small pruritic red papules that evolve into vesicles and pustules on the back, face, stomach, and chest before spreading to the extremities (Fig. 3). This centripetal spreading pattern is a characteristic feature of the evolution of the chicken pox exanthem [15]. The rash is often pleomorphic, and all of the various stages of the rash can be present at any one time.

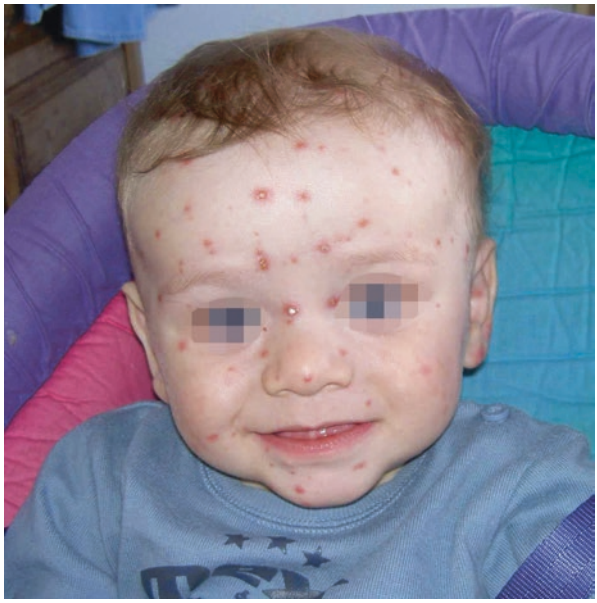

Fig. 3 Chicken pox in a child. (By Thomas Netsch; de.wikipedia.org: 13:13, 5. Mai 2005 . . Thomas Netsch (Diskussion) . . 1371 × 1384 (111021 Byte) (∗Beschreibung: Kleinkind mt Windpocken im Gesicht∗Quelle: selbst fotografiert am 14. Juni 2004 ∗Fotograf: Thomas Netsch ∗Lizenzstatus: Public Domain {{Bild-PD}}), Public Domain, https://commons.wikimedia.org/w/index.php?curid=171594)

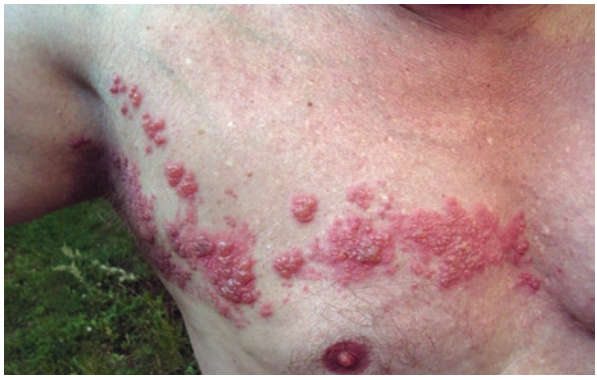

Fig. 4 Herpes zoster. (By Fisle - Fisle, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=2558194)

Pediatric patients 2 years and older can be treated with acyclovir 20 mg/kg/dose four times daily for 5 days. Acyclovir 800 mg PO four times daily for 5 days is the standard of care for adults with chicken pox [16].

Latent infection with the varicella zoster virus persists in the dorsal root ganglia after resolution of the active infection [17]. Reactivation of the latent virus causes herpes zoster or shingles infection. The clustered vesicular, pruritic, and erythematous rash is usually in the distribution of a single dermatome and does not cross the midline of the body [18] (Fig. 4).

Herpes zoster in children is generally painless, whereas in adults, it is painful and associated with an unpleasant prodrome similar to that experienced with chicken pox [18]. The pain associated with shingles can persist beyond resolution of the skin rash and is known as postherpetic neuralgia [18].

Herpes zoster is treated with acyclovir 800 mg five times daily for a period of 7–10 days [18]. Famciclovir 500 mg three times daily for 7 days or valacyclovir 1000 mg 3 times daily for 7 days has also been approved for treatment of shingles infections [18]. Postherpetic neuralgia is treated with gabapentin, non-opiate analgesics, opiates, low-dose amitriptyline, and topical anesthetic preparations [18].

Epstein-Barr Virus (HHV 4)

Epstein-Barr virus causes many infections resulting in disease processes ranging from multiple sclerosis to cancer. It, however, is best known for causing infectious mononucleosis. Its transmission is facilitated by exchange of saliva, tissue transplants, and blood transfusions between hosts. The seroprevalence of HHV 4 is approximately 90% of the adult population.

Mononucleosis affects almost all major organ systems in the body and has distinct cutaneous manifestations. The rash caused by EBV is an extensive, nonpruritic, maculopapular rash which may have morbilliform features. It predominates on the trunk and later spreads to involve the face and extremities [19] (Fig. 5).

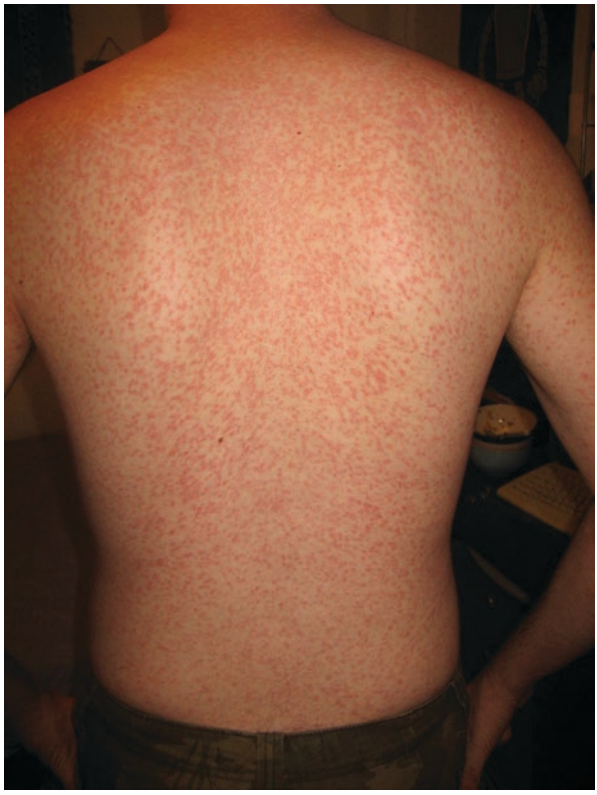

Fig. 5 EBV rash. (By Matibot - mine, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=8301675)

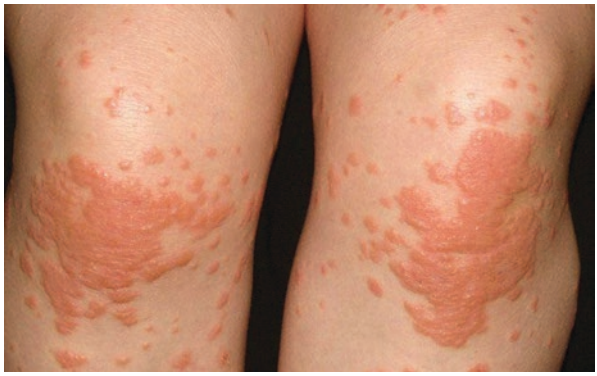

Fig. 6 Gianotti-Crosti (DermNet NZ)

EBV has also been implicated in precipitating a hypersensitivity reaction to beta-lactam antibiotics (penicillin derivatives, cephalosporins, monobactams, and carbapenems) in those suffering from infectious mononucleosis. A pruritic maculopapular morbilliform rash erupts and involves the entire body including the palms and soles [20]. The exanthem usually appears 5–8 days into the clinical course of the antibiotic treatment regimen. In the absence of active EBV infection, no hypersensitivity reaction is seen with beta-lactam antibiotics (see below).

Gianotti-Crosti syndrome (papular acrodermatitis of childhood) is a cutaneous manifestation of EBV seen in the pediatric population. It presents with a symmetrical, monomorphous, flat, pink-brown papule or papulovesicles 1–10 mm in diameter on the cheeks, buttocks, and extensor surfaces of forearms and/or legs [21]. The exanthem lasts for 10 days or more and is self-limiting (resolves in 15–60 days) and benign in its clinical course. There is no treatment for Gianotti-Crosti syndrome and interventions focus on relieving associated symptoms (Fig. 6).

HHV 6 and HHV 7

HHV 6 and HHV 7 are ubiquitous viruses worldwide. The seroprevalence of each virus in the adult population globally is as high as 95% [22, 23]. Infection with the virus usually occurs as a child and is easily transmitted from one host to another [24].

HHV 6 and HHV 7 have been implicated as causative agents in roseola infection. Sixth disease and exanthema subitum refer to the eruption of a rash that appears after the host experiences a sudden high fever (40 °C/104 °F) for approximately 3–5 days [24]. As the child defervesces, a non-pruritic, painless, blanching, maculopapular rash develops on the trunk which may spread to the extremities (Fig. 7). Small red papules on the soft palate (Nagayama spots) are also characteristic of roseola infection. This disease process is self-limiting, and treatment is supportive.

Reactivation of HHV 6 and HHV 7 is believed to cause pityriasis rosea [25–27]. This condition is characterized by the appearance of a large oval (2–5 cm in diam-

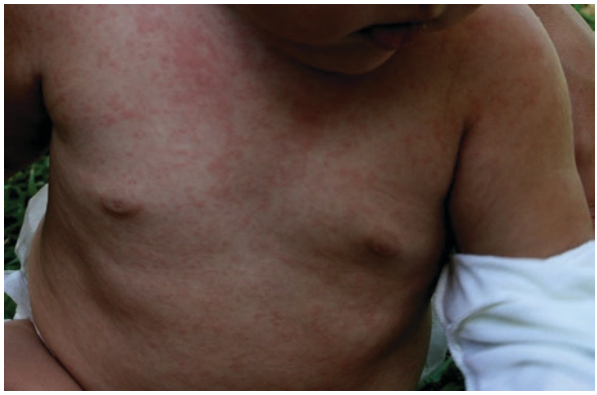

Fig. 7 Roseola. (WikiCommons Emiliano Burzagli)

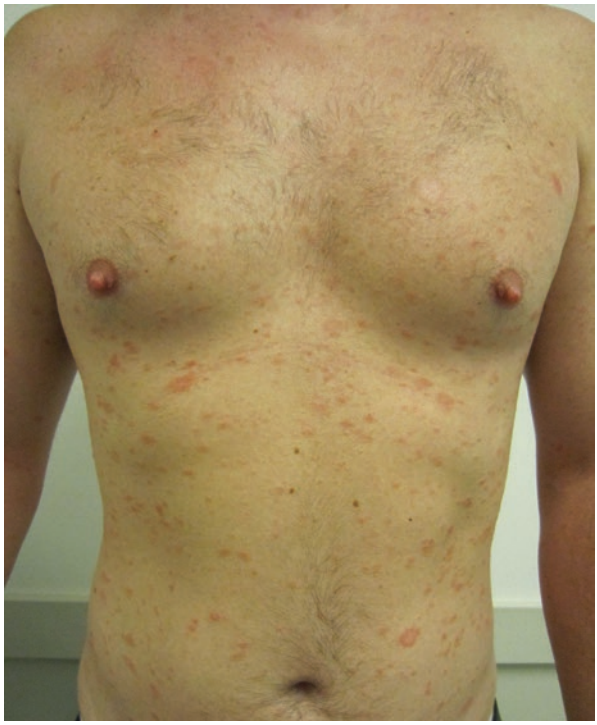

Fig. 8 Pityriasis rosea. (By James Heilman, MD – own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=16305229)

eter) salmon-colored "herald patch" prior to the eruption of smaller oval plaques [27]. The patch has a characteristic central clearing with fine scales on the periphery of the lesion oriented toward its center.

The smaller plaques are oriented along the lines of cleavage of the skin in a pattern referred to as a "Christmas tree" distribution [28] (Fig. 8). Over the course of the infection, the plaques desquamate, and a scaly flaky appearance predominates. The rash usually resolves after 6 weeks but can last for many months [28].

Management of pruritus and reassurance are the mainstays of treatment for most cases of pityriasis rosea.

Kaposi-Associated Herpesvirus (HHV8)

In regions of the world where HHV 8 is endemic (Mediterranean, Central Africa and East Africa), the seroprevalence of HHV 8 virus is between 10% and 70% in the adult population [29]. In regions where the virus is not endemic, the seroprevalence is typically <5% of the general population and predominates among men who have sex with men.

HHV 8 causes Kaposi sarcoma (KS) [30]. The cancer arises from cells that line the lymph and blood vessels. The cutaneous manifestations are cancerous tumors that are violaceous or dark brown/black macules, nodules, or patches that preferentially affect the distal portions of the lower extremities, toes, and feet [31] (Fig. 9). The lesions vary in size and can coalesce into larger plaques.

Kaposi sarcoma is classified into four subtypes:

1. Classic [32]: predominates in elderly men of Mediterranean, Central/Eastern European, and Middle Eastern ancestry. The progression of disease can be rapid with affected areas evolving over the course of weeks or slow and indolent with lesions remaining unchanged for months to years.
2. Endemic: very aggressive manifestation of KS. It has two subtypes:
   (a) African lymphadenopathic Kaposi sarcoma [32, 33]: affects the pediatric population worldwide (ages 10 and under) and is named based on the cohort of African children studied to characterize the disease.
   (b) African cutaneous Kaposi sarcoma [32]: endemic in parts of sub-Saharan Africa and affects men of ages 20–50. It presents with nodular vascular masses that affect the extremities [32].

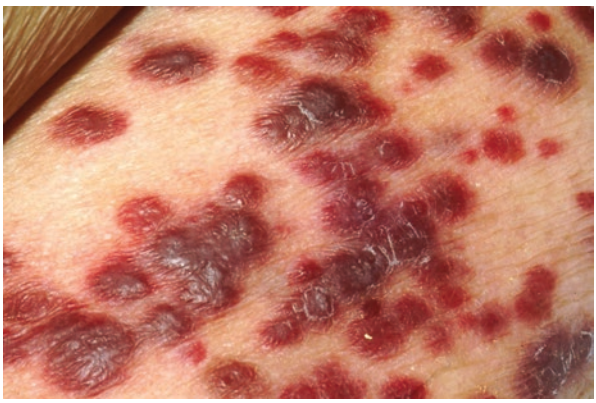

Fig. 9 Kaposi sarcoma lesions. (National Cancer Institute, public domain)

3. Iatrogenic [34]: occurs in the setting of immunosuppressive drug therapy. The KS tumors erupt if the host is infected with HHV 8 or receives an organ infected with HHV 8.
4. AIDS associated [35]: an AIDS-defining illness notable for its distribution on the mucus membranes, back, neck, trunk, and head.

There are no definitive treatment regimens for HHV 8 and by extension Kaposi sarcoma. Observation coupled with watchful waiting is the standard of care for those afflicted with the cancer. Surgery is generally not recommended but can be employed to achieve cosmetic results if lesions are disfiguring. Radiation therapy, cryotherapy, and laser ablation have also been used to achieve acceptable cosmesis [30]. In extensive disease and AIDS, cytotoxic chemotherapy with pegylated liposomal doxorubicin (PLD) is recommended [30, 31].

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Skin and Soft Tissue Infections

Anna Drapkin and Ingi Lee

The skin, which is the largest organ of the human body, is comprised of the epidermis, the dermis, and the subcutaneous fat. Below the subcutaneous fat layer is the fascia, which separates the skin from the muscle. The skin functions as the first-line of defense against infection. However, when this defense layer becomes compromised (e.g., trauma, excessive moisture, scratches, bug bites, central line placement), the host is at risk of developing an infection (Fig. 1).

Skin and soft tissue infections (SSTIs) can range from involving only the most superficial layer of the skin to the most serious skin infections that also involve the muscle. They are often caused by gram-positive organisms (e.g., *Staphylococcus* species and beta-hemolytic *Streptococci* species) which normally colonize the skin. Depending on the type of trauma and the patient's underlying comorbidities, other bacteria or fungi can also result in infection [2]. Management of SSTIs can include treatment with antimicrobial agents and surgical management as needed [1, 3].

Types of Skin and Soft Tissue Infections (SSTIs)

SSTIs are categorized as purulent or non-purulent infections. Purulent SSTIs are typically caused by *S. aureus*, while non-purulent infections are typically caused by beta-hemolytic *Streptococci* (including *Streptococci pyogenes*) [3]. This distinction

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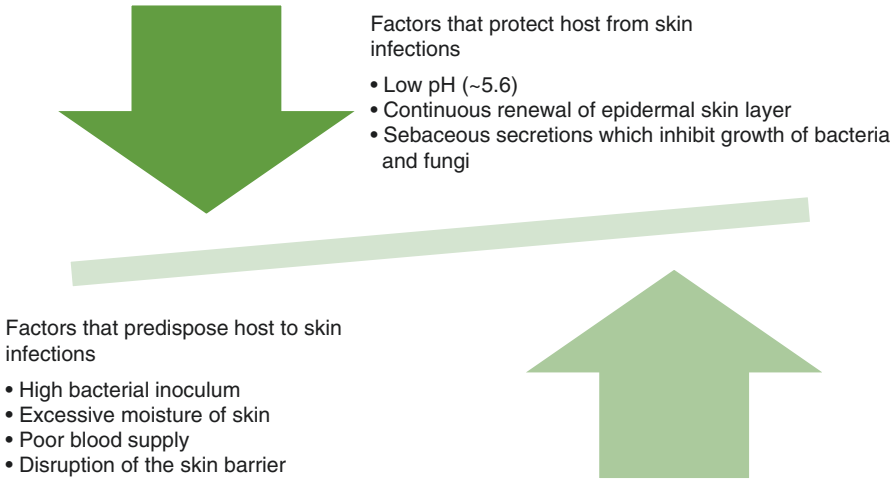

Fig. 1 Factors that influence development of skin infections [2]

can aid in decision-making regarding what antimicrobial therapy to initiate. This chapter will provide an overview of the management of the outpatient SSTIs including impetigo, folliculitis, cutaneous skin abscesses, erysipelas, and cellulitis.

Purulent SSTIs

Folliculitis

Folliculitis is the inflammation of the hair follicle. Although this is most commonly caused by a bacterial infection, non-infectious causes of folliculitis can also occur due to, for example, chemical irritation and physical injury [2]. The bacteria that is most commonly implicated in folliculitis is *S. aureus*, including MRSA. Risk factors for community-acquired MRSA (CA-MRSA) include people who live in close quarters (e.g., prisoners, military recruits), athletes, intravenous drug abusers, men who have sex with men, and those living in long-term care facilities [5].

Gram-negative bacteria are sometimes implicated in folliculitis, particularly *Pseudomonas aeruginosa*. *P. aeruginosa* lives in wet environments such as hot tubs and swimming pools. It forms biofilms, surviving on bathtubs, sponges, and pool toys [6]. Folliculitis associated with *P. aeruginosa* is typically acute (hours to days within exposure), beginning as a rash that progresses to pustules (Fig. 2). The rash is typically in the areas that were previously covered by a swimsuit [6]. Systemic symptoms such as fever, headache, and malaise may sometimes be present as well.

Folliculitis is usually self-limiting and resolves without the need for systemic antimicrobials. Patients who are immunocompromised, have persistent

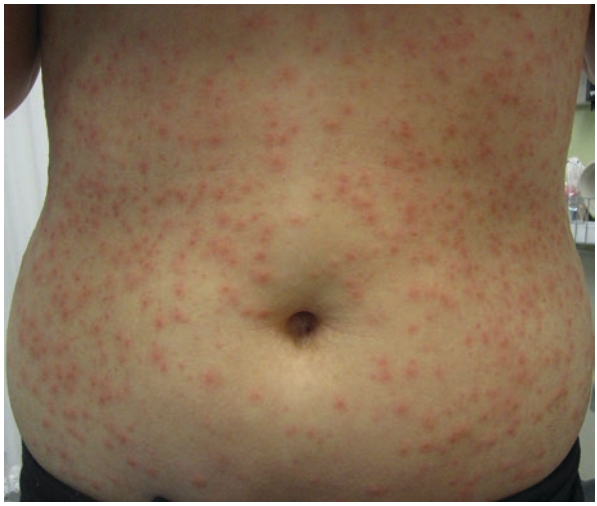

Fig. 2 Hot tub folliculitis. (WikiCommons, Dr. James Heillman)

fevers, or show evidence of systemic spread may require antimicrobial therapy similar to those used in the treatment of furuncles, carbuncles, and cutaneous abscesses [6].

Furuncles, Carbuncles, and Cutaneous Abscesses

While folliculitis is a superficial inflammation of hair follicles with pus present solely in the dermis, furuncles and carbuncles are infections that occur when infection spreads to the deeper layer of the skin. Furuncles are pus-filled abscesses that extend from the hair follicle to the subcutaneous tissue. Carbuncles are numerous furuncles which coalesce and extend even deeper into the subcutaneous skin layer [2, 3]. Cutaneous abscesses are painful, pus-filled nodules that form within the dermis (Fig. 3). The predominant bacterial offender of furuncles, carbuncles, and cutaneous abscesses is *S. aureus*. However, cutaneous abscesses can sometimes be polymicrobial, consisting of skin flora and organisms from neighboring mucous membranes by virtue of their location [3].

Treatment of folliculitis as well as small abscesses rarely requires systemic antimicrobial therapy. Observational studies and, most recently, randomized-controlled trials have both failed to demonstrate a significant difference in cure rates regardless of the utilization of systemic antibiotics [4]. Folliculitis and small furuncles may be treated with the application of warm compresses to promote drainage [3].

Large furuncles, carbuncles, and cutaneous abscesses should be treated with incision and drainage [3]. If the folliculitis requires surgical drainage where cultures can be obtained, the culture and antimicrobial sensitivity results should be used to guide the choice of antimicrobial agent given [4]. However, it is not always possible to obtain a culture.

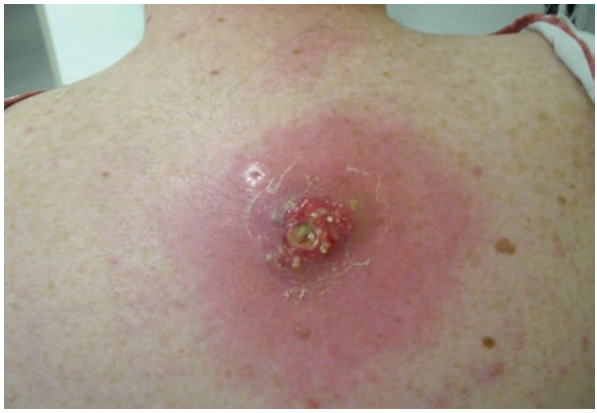

Fig. 3 MRSA skin abscess. (CDC, Greg Moran, MD)

Empiric systemic antibiotics active against MRSA may be considered for patients who have presence of systemic signs and symptoms of infection, have extensive abscesses covering a large surface area, and have either failed to respond adequately to incision and drainage or where adequate incision and drainage is not possible [3]. Patients who have hypotension in addition to the presence of systemic inflammatory reaction syndrome (SIRS) may require parenteral antibiotics and may not be candidates for outpatient therapy [3]. Table 1 lists antibiotic choices along with their respective spectrum in reference to SSTIs. As there are limited head-to-head trials comparing the efficacy of various antimicrobial agents in the treatment of SSTIs, the choice of antibiotic selection should be made on a case-by-case basis, accounting for patients' drug allergies, comorbidities, and drug-drug interactions. Treatment duration is typically approximately 7 days, depending on the patient's clinical response [3].

Non-purulent SSTIs

Erysipelas and cellulitis are diffuse, superficial infections of the skin that occur secondary to a breach in the skin barrier (e.g., an insect bite, trauma, or preexisting skin inflammation such as with eczema) [3]. The breach in the skin integrity may be unapparent from a small scratch or cracks in the skin between toe spaces. Erysipelas is an infection of the upper dermis and superficial lymphatics, as opposed to cellulitis which involves the dermis and subcutaneous fat [3]. Erysipelas usually presents as a sharply demarcated, burning erythema that is often found on the upper portion of the body [3, 9] (Fig. 4). In contrast, cellulitis is typically defined by the presence of unilateral poorly demarcated erythema, swelling, pain, and warmth often (but not always) found on the lower extremities [9] (Fig. 5). Bilateral lower extremity cellulitis is very rare, and when this occurs, differential diagnoses other than cellulitis should be strongly considered. Lymphatics are sometimes involved as well, which can lead to streaking and/or a pitting appearance of the skin, referred to as peau

Table 1 Antimicrobial therapy for SSTIs [3, 4]

Antibiotic regimen[a]	Active against CA-MRSA	Comments
Empiric antimicrobials targeting *S. aureus*		
Dicloxacillin 500 mg PO QID	No	Drug of choice for MSSA [2]
Cephalexin 500 mg PO QID	No	Drug of choice for MSSA in patients with delayed hypersensitivity to penicillin [2]
Doxycycline 100 mg PO BID	Yes	Pregnancy category D
Trimethoprim-sulfamethoxazole 1–2 DS tablets PO BID	Yes	Risk of acute renal failure and hyperkalemia, particularly in the elderly [4, 7] Pregnancy category C – may be considered when no safe alternatives exist in 2nd or 3rd trimester; avoid in 1st trimester and at term [8]
Clindamycin 300–450 mg PO QID	Yes	Diarrhea is the most common side effect; *Clostridium difficile* diarrhea may occur more often than with other oral agents [4]. Inducible resistance possible in MRSA [2, 4]
Linezolid 600 mg PO BID	Yes	More expensive compared to alternatives. Caution in patients currently taking serotonergic medications as the combination can result in serotonin syndrome. Long-term use associated with myelosuppression and peripheral neuropathies [4]
Empiric antimicrobials targeting beta-hemolytic *Streptococci*		
Penicillin VK 250–500 mg PO QID		Does not possess activity against *S. aureus*
Cephalexin 500 mg PO QID		May be used in patients with delayed hypersensitivity to penicillin
Clindamycin 300–450 mg PO QID		Alternative in presence of beta-lactam allergy [2]
Empiric antimicrobials targeting both beta-hemolytic *Streptococci* and *S. aureus*		
Cephalexin 500 mg PO QID		Does not provide coverage for MRSA
Dicloxacillin 500 mg PO QID		
Amoxicillin-clavulanate 875/125 mg PO BID		
Clindamycin 300–450 mg PO QID		Alternative in presence of beta-lactam allergy
Linezolid 600 mg PO BID		More expensive compared to alternatives. Caution in patients currently taking serotonergic medications as the combination can result in serotonin syndrome. Long-term use associated with myelosuppression and peripheral neuropathies [4]

Abbreviations: *PO* by mouth, *QID* four times daily, *MSSA* methicillin-susceptible *S. aureus*, *BID* twice daily, *MRSA* methicillin-resistant *S. aureus*
[a]Doses listed are for adults with normal renal function

d'orange (orange peel) [9]. Systemic signs and symptoms may also be present, such as fever and leukocytosis.

Evaluation and treatment of both erysipelas and cellulitis are the same. Cultures are not usually valuable for determining a bacterial culprit in non-purulent cellulitis.

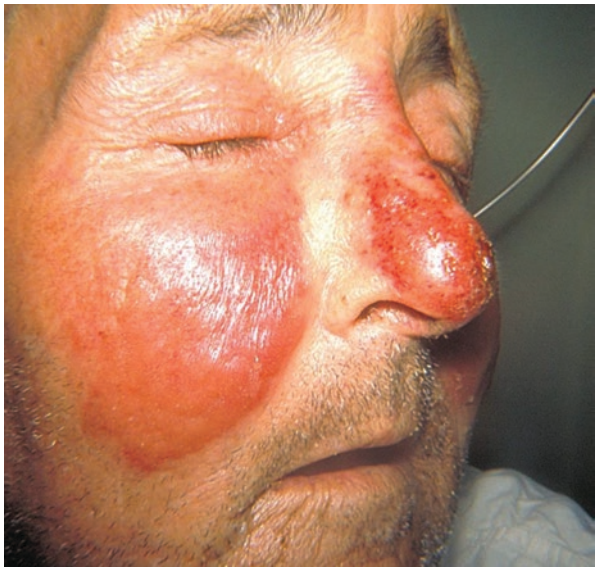

Fig. 4 Facial erysipelas. (CDC/Dr. Thomas F. Sellers)

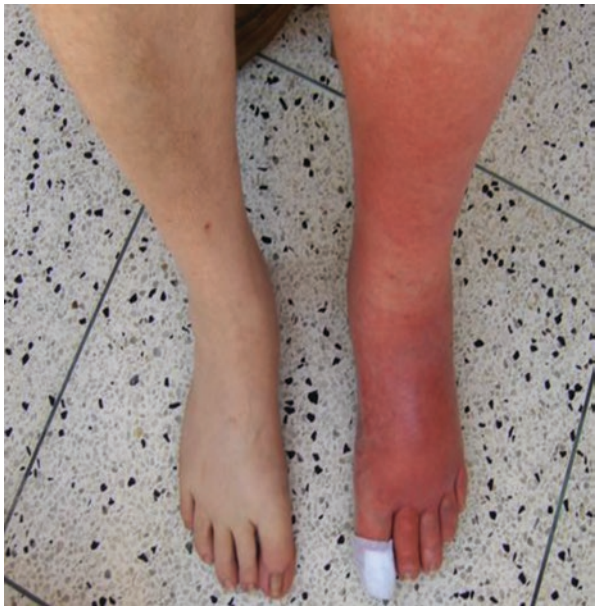

Fig. 5 Cellulitis left leg

Superficial skin swabs do not help in identifying the true cause of infection but rather reflect the flora colonizing the skin surface. For this reason, cultures are only recommended for pustules or abscesses once they are drained [3, 9].

Beta-hemolytic *Streptococci*, mainly *S. pyogenes* (Group A Strep), are responsible for most cases of non-purulent skin infections. *S. aureus* on the other hand is less often

implicated in these infections. Table 1 lists agents that are active against beta-hemolytic *Streptococci* and *S. aureus*. It is not advisable for doxycycline or trimethoprim-sulfamethoxazole to be used alone for the treatment of non-purulent SSTIs as they do not have activity against *Streptococci* species. If they are utilized, they should be combined with a beta-lactam (i.e., cephalexin, amoxicillin-clavulanate, or dicloxacillin). For the treatment of non-purulent cellulitis, there typically is no benefit in adding antimicrobials with activity against CA-MRSA for patients receiving cephalexin [10]. There are, however, a few exceptions. It may be prudent to provide empiric therapy for MRSA in patients presenting with cellulitis and any of the following risk factors: intravenous drug abuse, presence of an open wound, or a prior penetrating trauma [3]. Aside from *Streptococci* and *S. aureus*, infection due to other organisms is typically associated with special circumstances such as animal bites, injury that occurred in either freshwater or saltwater, and SSTIs that occur in immunocompromised patients.

Length of therapy is approximately 5 days depending on clinical progress [3]. If improvement does not occur within 5 days, the patient should be re-evaluated to ensure that there is no drainable collection present and the spectrum of the antimicrobial agent was appropriate and/or to evaluate for noninfectious causes (e.g., deep venous thrombosis).

Impetigo

Impetigo is an infection of the most superficial skin layer, the epidermis. Although any age group can be affected, it primarily affects young children. Outbreaks are commonly seen in areas with hot, humid weather given the environmental predisposition to microbial colonization [1]. The infection is highly contagious and spreads easily through skin-to-skin contact [2]. It can be classified into two categories: bullous impetigo and nonbullous impetigo.

Nonbullous impetigo, which accounts for the majority of impetigo cases, is characterized by small, pus-filled vesicles that quickly rupture [1]. Once ruptured, the purulent drainage from the vesicles dries to form honey-colored crusts (Fig. 6). The lesions which are generally painless can be pruritic, with scratching of the lesions leading to spread of infection [1]. The lesions are generally caused by *S. aureus* or *S. pyogenes* alone or a mixture of both organisms [1–3].

Bullous impetigo, which accounts for approximately 10% of all cases of impetigo, presents as a large, fluid-filled vesicle that progresses into bullae [1, 2]. These lesions primarily occur in neonates and young children but may also be seen in older children and adults [1, 2]. It is caused by a toxin-producing strain of *S. aureus*, which is responsible for the production of the fluid-filled vesicles [1–3].

Since nonbullous impetigo caused by *S. aureus* is clinically indistinguishable from that which is caused by *S. pyogenes* and cultures of lesions are not always feasible, empiric therapy should target both *S. aureus* and *S. pyogenes.* Topical mupirocin ointment applied twice daily to affected area for a duration of 5 days may be utilized in cases of limited lesions or in the absence of outbreaks [3]. In the pres-

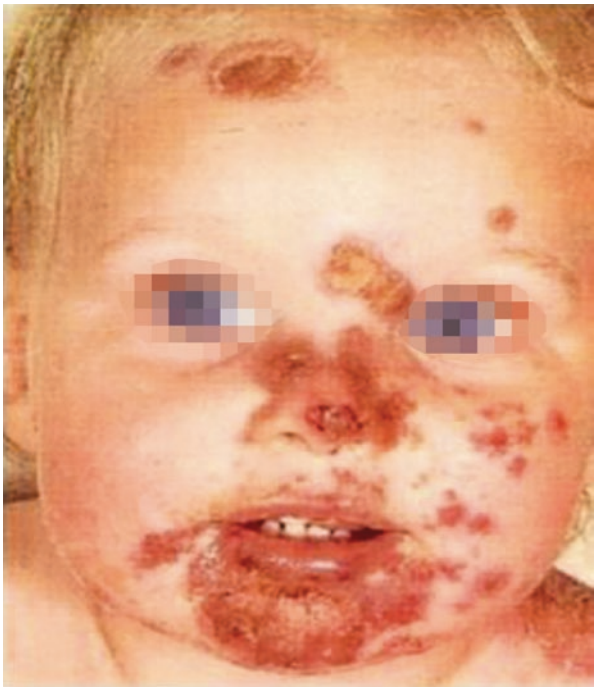

Fig. 6 Impetigo. (WikiCommons Pp90)

ence of multiple lesions or during outbreaks, oral therapy is recommended to reduce transmission of infection [3]. Since *S. aureus* isolates associated with impetigo are typically methicillin susceptible, empiric therapy with either dicloxacillin or cephalexin is recommended [3]. In instances when methicillin-resistant *S. aureus* (MRSA) is suspected or confirmed, therapy with clindamycin should be considered as it provides activity for both *S. pyogenes* and MRSA [3]. Treatment duration is approximately 7 days. If clinical improvement is not seen within this timeframe, microbial resistance should be considered [2].

Bullous impetigo is almost always caused by *S. aureus*; therefore empiric therapy with an antistaphylococcal beta-lactam is recommended. Mild-to-moderate cases of bullous impetigo can be managed with oral therapy [1]. In instances where extensive lesions are present, parenteral therapy should be considered. When there is high prevalence of MRSA in the community, an agent with activity against MRSA should be utilized (Table 1) [1].

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Seborrheic Dermatitis

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Epidemiology

Seborrheic dermatitis (SD) is considered one of the most commonly observed dermatological disorders in the United States [1–3]. The prevalence of SD is difficult to ascertain due to a lack of validated diagnostic criteria or severity scale. Reports indicate that 1–3% of the general US population and 43% of infants 1–3 months old are affected by SD [2–5]. SD has a biphasic incidence pattern that occurs in infants weeks to 12 months old and later during adolescence and adulthood. The peak incidence of SD in adults is between the third and fourth decades of life [2, 6]. SD affects a greater number of adult males than females, and it is believed to be associated with hormones [3, 6]. SD is commonly found in dry and cold climates [4, 5]. Patients with elevated levels of stress are at increased likelihood of developing SD [4–6].

SD is a common initial marker of immunodeficiency. It is prevalent among human immunodeficiency virus (HIV) and lymphoma patients and transplant recipients [6–8]. HIV patients with CD4+ T lymphocyte counts in the range of 200–500/mm^3 rarely display manifestations of SD [7, 9].

Various neurological and psychological disorders have been associated with SD, those being Parkinson's disease, transient ischemic attack (TIA), stroke, tardive dyskinesia, depression, spinal cord injury, traumatic brain injury, epilepsy, and facial nerve palsy [3–6, 10]. Congenital disorders such as Down's syndrome have also been identified to have an association with SD [4, 10, 11].

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Alexopoulos et al. found that children of mean age 3 months affected by SD had a family history of atopy, and main sites affected in these children were the face and scalp [12, 13].

Body Distribution

Seborrheic dermatitis primarily affects areas that have the greatest density of sebaceous glands, namely, the head and upper torso, in a symmetric distribution. On the head, this includes the brow, scalp, eyelashes, beard area (in men), nasolabial folds, and post-auricular creases. The external ear, but not its canal, may also be affected. In the trunk, this includes the presternum, inframammary areas, and upper back.

Pathogenesis/Pathophysiology

The pathogenesis of seborrheic dermatitis is not clearly understood as the underlying etiologic agent remains unknown. What is known is that there is a strong association of the disease with the yeast *Malassezia. Malassezia*, while an otherwise normal component of skin flora, invades the stratum corneum in those with seborrheic dermatitis and breaks down triglycerides and sebum into inflammatory fatty acids that result in scalp irritation and flaking [14–16]. This irritation further increases access of *Malassezia* into the stratum corneum in a progressive process [15, 16]. The effectiveness of antifungals in treating seborrheic dermatitis further lends validity to the belief of a fungal organism being a causative organism of the disease.

However, as the skin flora of most people contains *Malassezia*, there must be further etiological factors that allow the yeast to flourish in some more than others. Immunocompromised status is likely one of these, as the disease has a higher prevalence in those with HIV/AIDS [7, 17–19]. Furthermore, individuals with impaired immunological function due to certain genetic mutations, multiple comorbidities, or poor nutrition have a higher prevalence of SD [20, 21].

Despite these associations, however, the greatest prevalence of the disease lies in otherwise healthy individuals. It has been hypothesized that the disease is one of civilization, where human migration to indoor environments and increased clothing have resulted in a backup and blockage of the sebum that would otherwise have washed away by the elements [22–24]. This blockage may provide a more fertile ground for otherwise harmless *Malassezia* to flourish and become pathologic. The increased incidence of seborrheic dermatitis in persons with increased sebum pro-

duction (i.e., infants and teenagers) and in those with limited mobility (i.e., Parkinson's disease or bed-bound) further lends credence to this line of thinking [22–24].

Histology

Histologically, seborrheic dermatitis has several characteristic features. From deep to superficial, there is characteristic peri-follicular inflammation with resultant granuloma and/or lymphocyte infiltration, epidermal edema (spongiosis) around the superficial-most part of the hair follicle (infundibulum), retention of nuclei in the stratum corneum (parakeratosis) surrounding the opening (ostium) of the hairy follicle, and formation of keratinous plug [15, 25].

As the disease progresses to a more chronic state, it appears more similar histologically to psoriasis. There is a progression of the spongiosis and dermal inflammation of the superficial blood vessels that become dilated in a horizontal orientation [25–27]. This is associated with a more erythematous appearance of the disease clinically.

Clinical Presentation and Symptoms

Seborrheic dermatitis can affect any age group and is generally characterized by scaling and erythematous patches or plaques with wide variation in morphology based on patient age and area of skin involvement [28, 29]. It has a predilection for areas of high sebum production. In the early acute stages, it often results in scales covering moist areas. The scalp is almost always involved. Other sites of involvement can include the face, chest, intertriginous areas, and genital regions. Blepharoconjunctivitis can occur alone or with other conditions [28, 29]. Typically, patients may present with mild to moderate pruritus accompanying the rash.

Seborrheic dermatitis often has a characteristic appearance and distribution for different age groups. In infants, the distribution mainly involves the scalp and diaper area. In young children, the distribution can also involve the eyelids and eyelashes as well as the scalp. The distribution in adults can be more widespread involving different areas including the scalp, eyebrows, paranasal region and nasolabial folds, external auditory canals and post-auricular skin, chest, and groin (Figs. 1 and 2).

Infants with scalp involvement (cradle cap) present with greasy adherent plaques and scales involving the vertex of the scalp [30] (Fig. 3). Cradle cap appears during the first 3–4 months of life but usually resolves by 1 year of age. Young children can

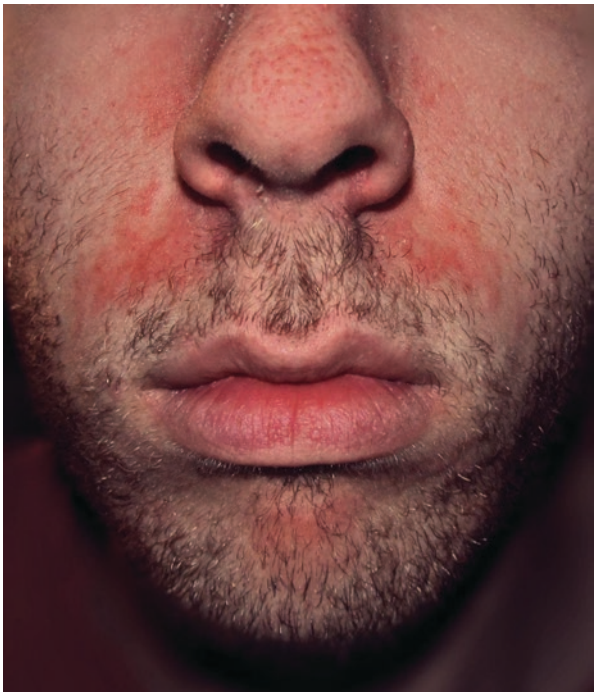

Fig. 1 Seborrheic dermatitis face. (Public Domain, WikiCommons)

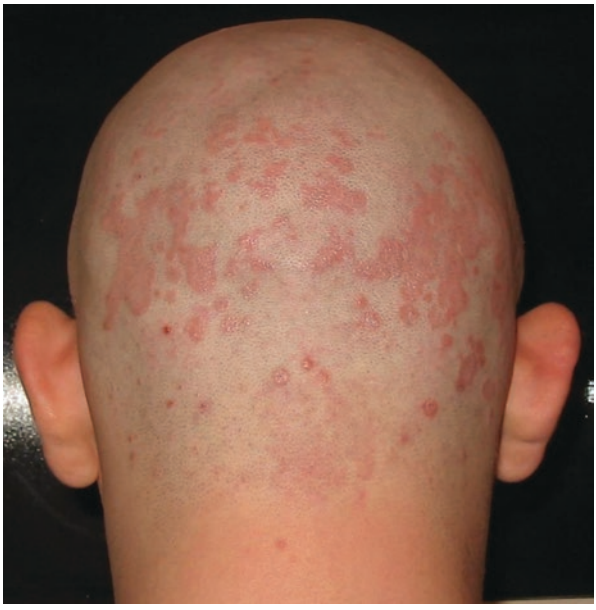

Fig. 2 Seborrheic dermatitis. (Public Domain Wiki Commons)

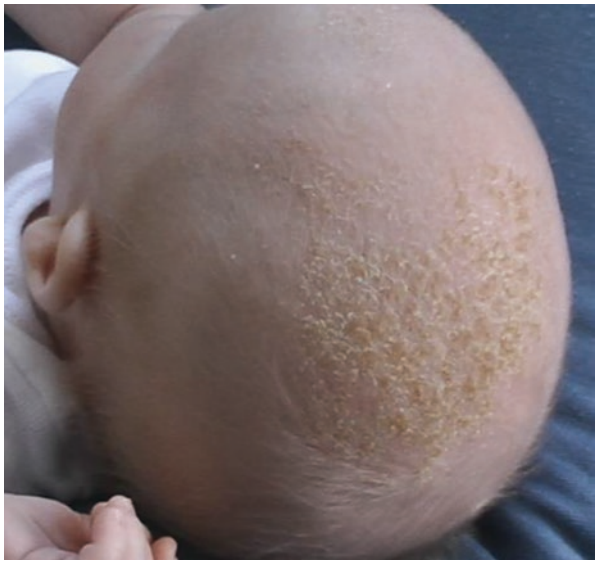

Fig. 3 Cradle cap. (CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=305422)

have a form of seborrheic dermatitis with scalp involvement called tinea or pityriasis amiantacea which presents as thick scales and flakes adherent to the tufts of the hair and scalp. This condition can often be confused with psoriasis, tinea capitis, or rarely atopic dermatitis [6].

Adolescents and adults are most commonly affected in the scalp with fine white dry flakes (dandruff) and pruritus. The flakes may progress to yellow crusts on an inflamed, erythematous base that can involve not only the scalp but also the forehead. As mentioned above, adults can have many other sites, or involvement in the presentation can be variable (papules, plaques, crusts).

Seborrheic dermatitis can be more severe in immunocompromised patients including those with human immunodeficiency virus, organ transplantation, and some forms of cancer. It is considered an early skin presentation of AIDS in both children and adults [9]. Seborrheic dermatitis in immunocompromised patients may be more extensive and severe than in immunocompetent patients. It often improves with effective antiretroviral therapy [7].

Seborrheic dermatitis is less common in African-American patients [31]. Seborrheic dermatitis has been associated with several conditions including Parkinson's disease, neuroleptic-induced Parkinsonism, tardive dyskinesia, traumatic brain injury, epilepsy, facial nerve palsy, spinal cord injury and depression, chronic alcoholic pancreatitis, hepatitis C virus, familial amyloidosis with polyneuropathy, and trisomy 21 (Down syndrome) [5, 10, 32–36]. It has also been associated with patients with psoriasis who had been treated with psoralen and ultraviolet A therapy [36].

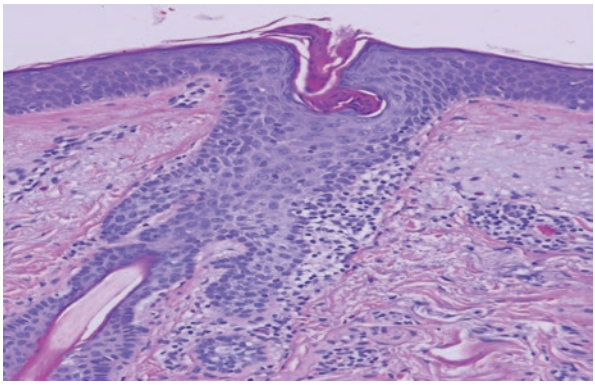

Fig. 4 Seborrheic dermatitis. A pilo-sebaceous apparatus (hair follicle with attached sebaceous gland and duct which empties into the follicle) is seen showing a lymphocytic infiltrate around the hair follicle and replacement of the hair shaft in the infundibulum with a keratotic plug containing retained nuclei from the underlying lining cells (parakeratosis) (hematoxylin and eosin, X310)

Diagnosis

The diagnosis of seborrheic dermatitis typically depends upon the recognition of the erythematous, greasy, scaling plaques in the classic distribution. So, the clinician relies on history and clinical examination to distinguish seborrheic dermatitis from other conditions. Rarely, a skin biopsy is required for accurate diagnosis. The differential diagnoses can include such conditions as psoriasis, atopic dermatitis, tinea cruris, acne rosacea, pityriasis rosea, lupus erythematosus, erythrasma, and HIV disease. In children, seborrheic dermatitis can be confused with tinea capitis. Sometimes it may be helpful to examine a superficial skin scraping prepared with potassium hydroxide by microscopy to rule out tinea capitis. Rare conditions that can sometimes mimic seborrheic dermatitis include Langerhans' cell histiocytosis, dermatomyositis, Wiskott-Aldrich syndrome, zinc deficiency, glucagonomas, and histiocytosis X in infants [6] (Figs. 4 and 5).

Treatment

There are various methods of treating SD. The treatment of SD focuses on the clearing signs of the disease particularly pruritus as well as maintaining a prolonged state of remission. The most common mechanisms of action for targeted

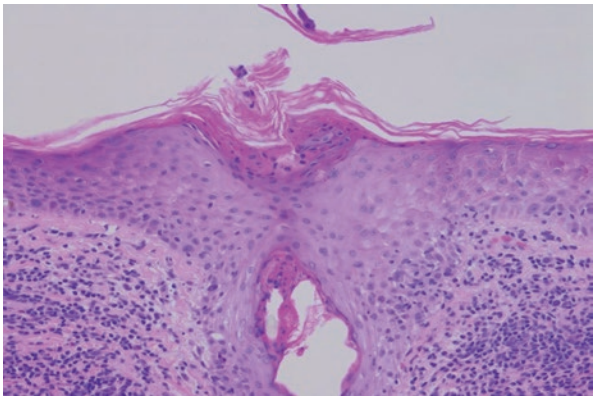

Fig. 5 Seborrheic dermatitis, a more severe lesion than shown in Fig. 3 that shows, additionally, a more severe lymphocytic infiltrate containing also small dilated blood vessels running parallel to the surface. There is also a keratotic plug extending into the ostia (surface) with cellular debris and neutrophils (hematoxylin and eosin, X310)

therapy include reducing the inflammatory process, pruritus, and erythema, as well as inhibiting yeast colonization, and loosening of scales [3–6]. The most commonly utilized treatments are antifungals and anti-inflammatory. Table 1 displays the various therapies in categories based upon their mechanism of action.

Topical antifungals are utilized to decrease the inflammatory response and proliferation of *Malassezia* in SD. Antifungals can be utilized on all skin types and infants safely. An investigator-blinded randomized controlled trial with 325 patients with moderate to severe scalp SD found that a combination of clobetasol propionate 0.05% shampoo twice weekly alternated with ketoconazole (KC) 5% shampoo twice weekly was more effective than KC alone [37]. A randomized trial comparing the non-inferiority efficacy and tolerance of 2% miconazole nitrate shampoo versus 2% KC discovered that miconazole is at least as effective and safe as KC. There is no statistical significance with the short-term (<4 weeks) use of steroid therapy and calcineurin inhibitor therapy for complete clearance of the affected scalp or face [38]. Evidence indicates that treatment of the scalp or face with lithium salts results in total clearance more often than with use of azoles, yet similar rates of adverse events are reported [38]. A double-blind randomized trial of 72 patients evaluating the efficacy of moistures in infants found that licochalcone improved the affected SD area by 42% versus 1% hydrocortisone.

Table 1 Categories, formulations, mechanisms of action, and adverse effects of therapies for SD

Category		Formulations	Mechanism of action	Adverse effects	Cost ($USD)	References
Antifungals	*Azoles*	*Ketoconazole* (Nizoral, Xolegel) – 2% shampoo, cream, gel, 200 mg tablets *Itraconazole* (Sporanox) – 100 mg tablets *Miconazole nitrate* – 2% shampoo	Inhibits synthesis of ergosterol (component of fungal cell wall) and 5-lipoxygenase	*Ketoconazole* – hypersensitivity; angioedema; burning at application site and headache *Itraconazole* – hepatotoxicity; pancreatitis; congestive heart failure; pulmonary edema; hypersensitivity reaction *Miconazole* – irritation; pruritus; erythema; contact dermatitis	2% shampoo (120 mL) – $30 2% topical foam (50 g) – $195	[4, 14, 15]
	Allylamines	*Terbinafine* (Lamisil) 1% gel cream, solution, 250 mg tablets	Inhibits squalene epoxidase (fungal cell wall synthesis)	Rash, elevated AST/ALT, photosensitivity	1% gel – $10	[3, 4, 6, 15]
	Benzylamines	*Butenafine* (Mentax) – 1% cream	Inhibits squalene epoxidase (fungal cell wall synthesis); able to diffuse into sebum; anti-inflammatory	Burning or skin irritation, at the application site	1% cream – $200	[3, 4, 6, 15]
	Hydroxypyridines	*Ciclopirox*: 0.77% cream, 1% cream, shampoo, solution	Anti-inflammatory; inhibits prostaglandin and leukotriene synthesis	Skin irritation or discoloration at the application site	0.77% gel (30 g) – $24	[3, 4, 6, 10, 15]
Antifungals	*Zinc pyrithione*	1% and 2% shampoo, 1% cream	Reduces epidermal cell turnover (cytostatic); antifungal and antibacterial mechanism of action unknown	Skin irritation	(Ketoconazole/ zinc pyrithione) – 2%/1% (50 mL) – $14	[3, 4, 6, 10, 15, 20]
	Selenium sulfide	(Selsun) shampoo 1%, 2.25%; 2.5% lotion	Reduces epidermal and follicular epithelial corneocyte production (cytostatic); antifungal mechanism of action unknown	Alopecia, skin irritation, hair discoloration, hyperpigmentation (rare)	2.25% of selenium sulfide shampoo (180 ml) – $ 39	[4, 6, 10, 15]
	Tea tree oil	5% suspension	Hypothesized that antifungal; impacts cell wall synthesis and cell wall permeability	Irritant contact dermatitis; estrogenic and anti-androgenic effects limit use	1 FL oz. – $11	[4, 20, 21]

Topical corticosteroids	Hydrocortisone Betamethasone Clobestol-17-butyrate Clobetasol dipropionate Desonide	Anti-inflammatory; immunosuppressive; anti-mitogenic	Skin atrophy; telangiectasias; folliculitis; Hypertrichosis	Variable $32–$144	[3, 4, 6, 10, 15]
Topical calcineurin inhibitors	Pimecrolimus Tacrolimus	Unclear; suspect inhibits T lymphocyte activation	Transient burning sensation at application site; pruritus	Pimecrolimus 1% (30 g) – $204 Tacrolimus 0.1% (30 g) – $234	[3, 4, 6, 10, 15, 19]
Antibiotic	Metronidazole 0.75% topical lotion or gel	Exact MOA unknown; inhibits nucleic acid synthesis; disrupts anaerobes DNA (bactericidal)	Contact sensitization	Lotion (59 mL) – $220 Gel (59 mL) – $100	[3, 6, 10, 15]
Tar	0.5% coal tar shampoo	Decreases inflammatory response; decreases sebum production	Focal folliculitis, contact dermatitis of the fingers, exacerbation of psoriasis in affected individuals, local skin atrophy, telangiectases, pigmentation, exfoliative dermatitis, and keratoacanthomas	120 mL – $9 235 mL – $10 251 mL – $10	[3, 6, 10, 15]
Phototherapy		Unclear	Burning, itching; prolonged use increases risk of malignancy	Variable – average $250 per treatment	[3, 10, 15]

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Tinea Infections: From Head to Toe

Maya Bass

Introduction

Superficial tinea infections are the most commonly misdiagnosed infection by primary care physicians. It is also the most common of all mucocutaneous infections. The prevalence of superficial tinea infections is 20–25%. Age of onset varies by type of tinea infection with scalp infections typically infecting young children and up to 50% of patients over the age of 75 years having onychomycosis. It affects all races although tinea capitis is found more commonly in black children, and black adults have a lower incidence of dermatophytosis in general. Tinea infections are typically contracted by contact with fomites, infected individuals, and animals. It can also be contracted from the soil. Given its common nature and ease of treatment, it is crucial for the primary care physician to become well versed in diagnosis of these infections.

Etiology

There are three genera of dermatophytes:

1. *Trichophyton*
   (a) This type is found in the hair, skin, and nails. *T. rubrum* is the most common cause of tinea infections. Seventy percent of the US population will experience *T. rubrum* infection, typically as tinea pedis, in their lifetime.
2. *Microsporum*
   (a) This type is typically found on the skin and hair.

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3. *Epidermophyton*

   (a) This type is most commonly found in the nail.

It should also be noted that the "tinea" versicolor infection that will be described in this chapter is not caused by one of the above pathogens but rather by a yeast, *Malassezia*.

Tinea Infections from Head to Toe

Tinea infections affect the entire body, at different ages, and are treated differently. To guide understanding, this chapter will be organized by location.

Tinea Capitis

Epidemiology

Tinea capitis affects children aged 6–10 years. It is much less common in patients over 16 years of age, unless in a rural population. It is more common in black children when compared to white populations. It can become an epidemic in schools due to close contact. Ninety percent of tinea capitis infections in the USA and Western Europe are due to *T. tonsurans*. It is most commonly transmitted from fomites or contact with the infected person or animal. It can be contracted from spores as well. Risk factors include being immunocompromised, having chronic disease, and malnutrition.

Body Distribution

Typically only infects the hair follicles of the scalp.

Symptoms

Tinea capitis can present with superimposed inflammation or without. Without inflammation, patients will complain of scalp pruritus, scaling, alopecia, or occipital or posterior auricular adenopathy. With formation of a kerion, the term used to describe inflammatory tinea capitis, symptoms will include pain, crusting, and, on occasion, alopecia or purulent discharge.

Diagnosis

Diagnosis can be made from clinical exam. Laboratory examination includes microscopy, Wood's lamp examination, and fungal cultures. Dermatopathology is typically unnecessary.

- Microscopy: Remove of broken hair by forceps and obtain skin scales with a cervical brush. Place the hair and on a microscope slide. The sample is prepared using potassium hydroxide 5–20% solution. The provider is looking for septated, tubelike structures that represent hyphae.
- Wood's lamp: Hairs infected with Microsporum will illuminate with green fluorescence in a darkened room. However, 90% of the tinea capitis in the USA is *T. tonsurans* and will not react to Wood's lamp.
- Fungal cultures: Specimens can be collected as described above and placed in a fungal culture. This is recommended to be repeated monthly.

Description

Typically a round hyperkeratotic plaque of alopecia with evidence of broken hair shafts or "black dot alopecia." A scale may be present (Fig. 1). The area and plaque will have a green fluorescence with Wood's lamp examination. In the case of a "kerion," it will be associated with inflamed nodes, possibly a purulent discharge, thick plaques, crusting, and loose hairs.

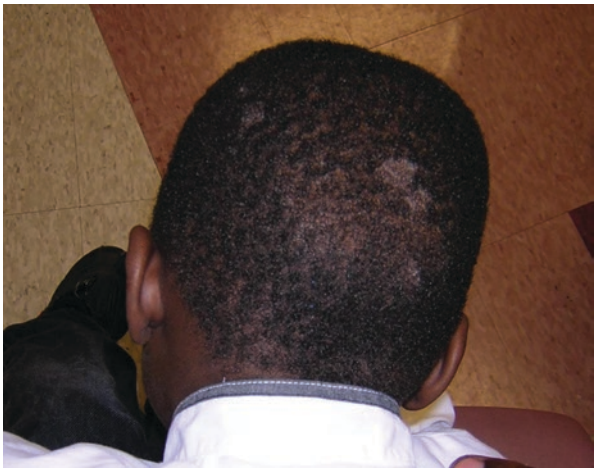

Fig. 1 Typical "black dot" lesions seen on the scalp of a child. Tinea capitis (119_tine_capi_hr). (Jefferson Clinical Images Database [4])

Differential

This can be mistaken for seborrheic dermatitis, psoriasis, lichen simplex chronicus, and alopecia areata.

Treatment

Treatment requires oral antifungals as topical agents alone are ineffective. However, evidence shows that concomitant treatment with topical agents can decrease transmission rates. These agents include 1% or 2.5% selenium sulfide (Selsun Blue) shampoo or 2% ketoconazole shampoo. Topical treatment is only required for the first 2 weeks.

If a kerion is present, adjuvant therapy with systemic prednisone (1 mg/kg per day for 14 days for children) can be used for painful kerions. Systemic antibiotics should also be used if superinfection is present. Antibiotics with coverage of *S. aureus* and GAS should be used (Table 1) [1–3, 5, 6].

Tinea Barbae

Epidemiology

Only seen in adult males. Typically caused by *T. verrucosum* and *T. mentagrophytes*. Occasionally acquired through animal exposure.

Table 1 Treatment of tinea capitis

Agent	Pediatric dose	Adult dose
Griseofulvin First line	20–25 mg/kg per day (max 500 mg/day) for 6 weeks or more based on resolution	250 mg BID for 1–2 months If "black dot" may require longer course
Terbinafine For ages greater than 4 years	<25 kg (55 lb):125 mg/day 25–35 kg (55–78 lb): 187.5 mg/day >5 kg (78 lb): 250 mg/day	250 mg/day for 6 weeks
Itraconazole Not FDA approved for this use but approved for older than 6 months. Some RCTs exist showing good efficacy	5 mg/kg per day for 4–8 weeks 10 mg/kg if evidence of systemic effects	200 mg/day for 4–8 weeks
Fluconazole	6 mg/kg per day. Daily for 2 weeks. Repeat in 4 weeks if necessary	200 mg/day for 4–6 weeks

Body Distribution

This is found in distribution of a beard or mustache. Occasionally eyebrows and eyelashes can be involved.

Symptoms

Tinea barbae typically presents with pruritus, tenderness, and pain.

Diagnosis

Diagnosis can be made from clinical exam. Laboratory examination includes microscopy, Wood's lamp examination, and fungal cultures.

- Microscopy: Removal of broken hair by need holder of forceps and obtaining skin scales with a cervical brush. Placing the hair on a microscope slide. The sample is prepared using potassium hydroxide 5–20% solution. The provider is looking for septated, tubelike structures that represent hyphae.
- Wood's lamp: Hairs infected will illuminate with green fluorescence in a darkened room although not likely with the *Trichophyton* species.
- Fungal cultures: Specimens can be collected as described above and placed in a fungal culture. This is recommended to be repeated monthly.
- Of note: Superinfection with staph species is common and does not exclude diagnosis of tinea barbae.

Description

Tinea barbae lesions include erythematous papules typically involving hair follicles. The hairs will be loose. There can be purulent drainage. Lesions can also appear as scaling erythematous annular patches. It is possible for lesions to form a kerion.

Differential

This can be mistaken for acne vulgaris, folliculitis, carbuncle, or furuncle.

Table 2 Treatment of tinea barbae

Agent	Dose
Griseofulvin	250 mg BID for 1–2 months If "black dot" may require longer course
Terbinafine	250 mg/day for 6 weeks
Itraconazole	200 mg/day for 4–8 weeks
Fluconazole	200 mg/day for 4–6 weeks

Treatment

Treatment requires oral antifungals as topical agents are ineffective. Systemic antibiotics should also be used if superinfection is present. Antibiotics with coverage of *S. aureus* and GAS should be used (Table 2) [1–3].

Tinea Corporis

Epidemiology

Tinea corporis affects all ages and is most commonly caused by *T. rubrum*. It can also be caused by *T. tonsurans* in parents of children with tinea capitis. Transmission is caused by autoinoculation or contact with another person. Lesions in areas of the body that touch such as the axilla or thighs can cause "kissing" lesions. It is commonly seen in tropical and subtropical regions. People who work with animals are also at an increased risk.

Body Distribution

Infection of the neck, trunk, and extremities excluding the hands, feet, and groin.

Symptoms

Typically it presents with pruritus and scaling lesions.

Diagnosis

Diagnosis can be made from clinical exam. Laboratory examination includes microscopy, Wood's lamp examination, and fungal cultures. Dermatopathology is unnecessary.

- Microscopy: Obtain skin scales by scraping lesion with a #15 blade. Place on a microscope slide. The sample is prepared using potassium hydroxide 5–20% solution. The provider is looking for septated, tubelike structures that represent hyphae.

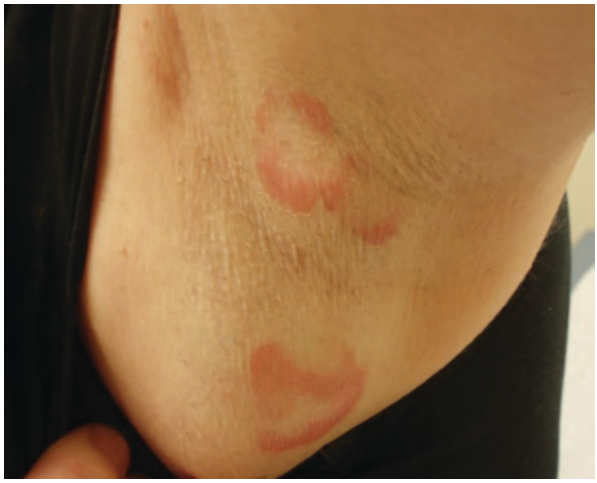

Fig. 2 "Kissing lesions" seen when self-inoculation causes multiple annular lesions with central clearing. Tinea corporis of the axillary (792_tineascorp_axilla_hr). (Jefferson Clinical Images Database [4])

- Wood's lamp: Lesions will illuminate with green fluorescence in a darkened room, but the *T. rubrum* would not react.
- Fungal cultures: Specimens can be collected as described above and placed in a fungal culture.

Description

Typically it presents as a round scaling, well-demarcated plaque. Occasionally, vesicles or pustules will be present at the margin. Typically, there is a central clearing (Fig. 2). Lesions can also take on a psoriasiform plaque. Sometimes lesions can have a vesicular presentation (Fig. 3).

Differential

This can be mistaken for atopic dermatitis, annular erythemas, psoriasis, seborrheic dermatitis, contact dermatitis, the herald patch of pityriasis rosea, tinea versicolor, erythema migrans, subacute cutaneous lupus, and granuloma annulare.

Treatment

Usually, topical agents are sufficient. Systemic therapy can be considered if infection has failed to respond to topical preparations. All agents should be applied BID for about 4 weeks. Topical treatment needs to be continued for at least 1 week after resolution of a lesion. Treatment should also extend over the margin of the lesion. Please note that nystatin is not a recommended therapy for topical tinea infections.

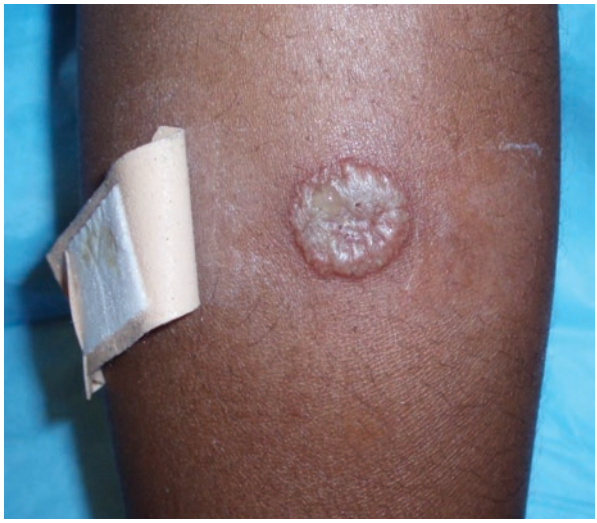

Fig. 3 Vesicular tinea corporis of the forearm. (Jefferson Clinical Images Database [4])

Table 3 Treatment of tinea corporis

Agents	Options	
Best agents	Terbinafine (Lamisil)	1% cream
	Butenafine (Lotrimin Ultra)	1% cream
Other agents	Imidazoles	Clotrimazole Miconazole Ketoconazole Econazole Oxiconazole Sertaconazole
	Allylamine	Naftifine
	Naphthenates	Tolnaftate
	Substituted pyridone	Ciclopirox olamine

A meta-analysis and a Cochrane review evaluated the many different topical agents available. Based on these RCTs, butenafine and terbinafine are superior based on increased sustained cure and decreased adverse effect. Studies on the use of combination therapy of topical steroids with topical antifungals are inconclusive, and there is no specific guideline established (Table 3) [1–3, 8–10, 12].

Tinea Versicolor, Now Known as Pityriasis Versicolor

Epidemiology

This infection is caused by *M. furfur,* which is a yeast not a dermatophyte. It typically affects patients starting at puberty, through young adulthood, and is less common in patients over the age of 60. It is exacerbated by warm seasons, exercises, oily

skin, use of cocoa butter, glucocorticoid treatment, and immunodeficiency. For most patients, it will occur only in summer months. In patients who sweat consistently, year round, like athletes, it can persist even in the winter months.

Body Distribution

This infection can be found anywhere on the body. It is most common in areas with high sebaceous gland activity.

Symptoms

This infection is asymptomatic or mildly pruritic. Patients will seek care due to discoloration of their skin.

Diagnosis

Diagnosis can be made from clinical exam. Laboratory examination includes microscopy and Wood's lamp examination.

- Microscopy: scraping of lesion and placing in KOH preparation will show round yeasts and pseudohyphae to create a "spaghetti and meatballs" appearance.
- Wood's lamp: scaled lesions can have green fluorescence in a darkened room. The *Malassezia* should react to the light.

Description

It appears as sharp margined macules that will vary in size. Lesions can range from light brown to dark brown typically becoming hypopigmented on tanned skin. There is typically a very fine scale that can only be appreciated with scraping (Fig. 4).

Differential

The differential includes vitiligo, pityriasis alba, pityriasis rosea, nummular eczema, and post-inflammatory hypopigmentation.

Treatment

Topical agents are the treatment of choice (Table 4) [1–3].

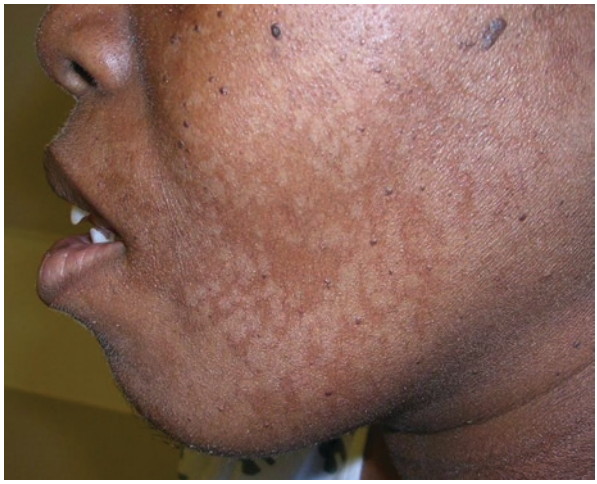

Fig. 4 Tinea versicolor. Hypopigmented circular lesions seen. Tinea versicolor (337_pit_oval_hr_1). (Jefferson Clinical Images Database [4])

Table 4 Treatment of tinea versicolor

Agent	Dose
Selenium sulfide shampoo or lotion	2.5%. Apply daily for 1 week. Applied to lesions for 10–15 min prior to showering. Prophylaxis: 1–2 weekly
Ketoconazole shampoo	Daily for 1 week Prophylaxis: 1–2 weekly
Terbinafine	1% solution BID for 7 days
Azole creams	BID for 2 weeks

Tinea Cruris

Epidemiology

Tinea cruris typically affects male adults and is caused by *T. rubrum* during warmer months. Other risk factors include tight clothing, obesity, and topical glucocorticoid application. It is most commonly associated with a concurrent tinea pedis infection.

Body Distribution

It is found in the groin, upper thighs, and buttock. It typically does not extend to the penis or scrotum.

Symptoms

Tinea cruris presents with pruritus of the region but can be asymptomatic.

Diagnosis

Diagnosis can be made from clinical exam. Laboratory examination includes microscopy and Wood's lamp examination.

- Microscopy: One can obtain skin scales with a 15 mm blade. Place sample on a microscope slide. The sample is prepared using potassium hydroxide 5–20% solution. The provider is looking for septated, tubelike structures that represent hyphae.
- Wood's lamp: The lesions do not typically have any fluorescence. However, the lack of coral-red fluorescences helps to exclude erythrasma as a diagnosis.

Description

The lesions are well-demarcated, large, scaling plaques. The color ranges from red to brown. There is commonly a central clearing. Occasionally pustules are present at the edge of the lesion (Fig. 5).

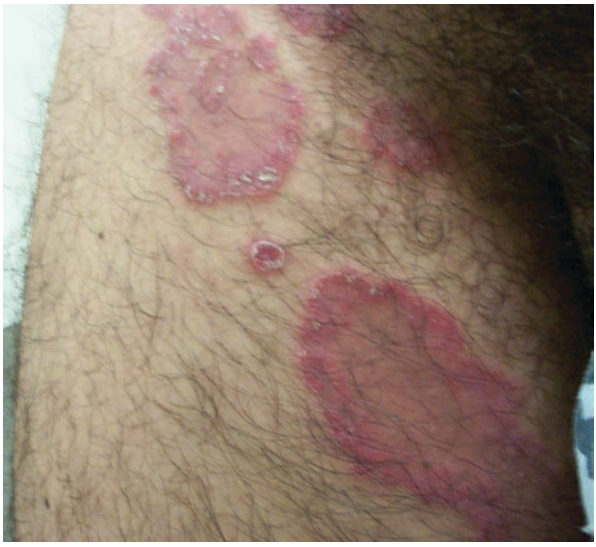

Fig. 5 Tinea cruris. Well-demarcated red annular lesions found in the groin. Tinea cruris (25_tine_cru1-hr). (Jefferson Clinical Images Database [4])

Differential

This can be mistaken for erythrasma, intertrigo, candidiasis, and psoriasis.

Treatment

Treatment is typically topical agents and shows a similar success profile to those used to treat tinea corporis [7]. As with tinea corporis, treatment should extend past resolution of the lesions with a minimum course of 10 days. Systemic treatment is only necessary if lesions do not resolve with topical agents or if the lesions are extensive (Table 5) [1–3, 11, 12].

Tinea Pedis

Epidemiology

Tinea pedis most commonly affects male adults aged 20–50 years. Risk factors include hot, humid weather, excessive sweating, occlusive footwear, and walking barefoot on contaminated areas.

Table 5 Treatment of tinea cruris

Agents	**Options**	
Best topical agents	Terbinafine (Lamisil)	1% cream
	Butenafine (Lotrimin Ultra)	1% cream
Other topical agents	Imidazoles	Clotrimazole Miconazole Ketoconazole Econazole Oxiconazole Sertaconazole
	Allylamine	Naftifine
	Naphthenates	Tolnaftate
	Substituted pyridine	Ciclopirox olamine
Best oral agent regimens	**Agent**	**Dose**
	Fluconazole	50 mg–100 mg daily or 150 mg weekly for 2–3 weeks
	Itraconazole	Either 100 mg/day for 2 weeks or 200 mg/day for 1 week
	Terbinafine	250 mg/day for 1–2 weeks
	Griseofulvin	250 mg TID for 2 weeks

Body Distribution

Tinea pedis affects interdigital areas and soles of the feet most commonly.

Symptoms

Tinea pedis presents with peeling skin or mild pruritis of the feet.

Diagnosis

Diagnosis can be made from clinical exam. Laboratory examination includes microscopy, Wood's lamp examination, and fungal cultures.

- Microscopy: KOH prep of a sample from the inner aspect of a vesicle is best but can be done from skin scrapings. Slides will allow providers to detect hyphae.
- Wood's lamp: A lack of coral-red fluorescence excludes erythrasma.
- Fungal cultures: Specimens taken from peeking lesions only produce dermatophytes in less than 30% of cases. Bacterial cultures can be taken if there is evidence of superinfection.

Description

Tinea pedis has a variety of patterns. The interdigital type (Fig. 6) presents between the toes as dry scaling. The moccasin type (Fig. 7) presents as scaling, hyperostosis, and papules at the well-demarcated margins of the feet, typically

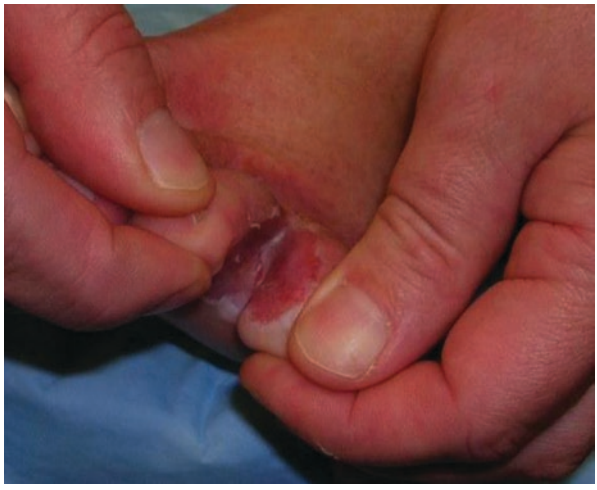

Fig. 6 Interdigital tinea pedis. Peeling in between the fourth and fifth digits. Tinea pedis (407_tin_pedis_hr). (Jefferson Clinical Images Database [4])

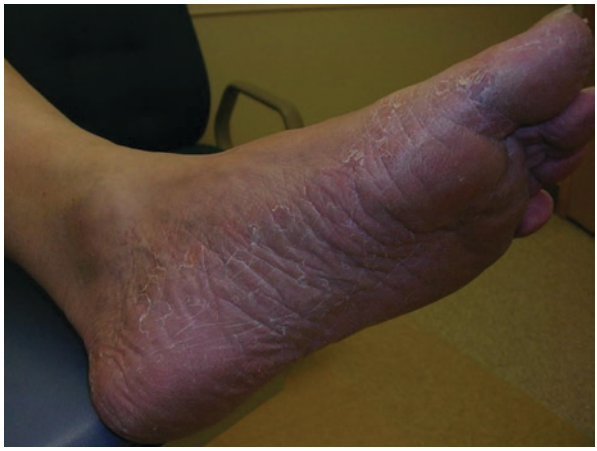

Fig. 7 Moccasin-type tinea pedis. Dry scaling seen along the sole and edge of the foot. Tinea pedis (418_Tine_ped_hr). (Jefferson Clinical Images Database [4])

confined to the sole of the feet. Vesicles or bullae are possible when there are concurrent superinfections.

Differential

This appears similar to erythrasma, impetigo, candidiasis, psoriasis, eczematous dermatitis, and pitted keratolysis.

Treatment

Treatment combines a topical agent with prevention. Patients should be encouraged to use shower shoes at home and in public. Feet should be washed with benzoyl peroxide directly after showering. Special concern should be given to those with impaired peripheral blood flow (i.e., diabetics) as they are at risk for developing secondary infections. Oral regimens are recommended for moccasin type or those who fail initial therapy (Table 6) [1–3, 8].

Tinea Unguium/Onychomycosis (ICD 10:B35.1)

Epidemiology

Onychomycosis affects all ages with a minor increased prevalence in males. There is an increasing incidence with age as it does not remit spontaneously. It is typically caused by *T. rubrum* and *T. mentagrophytes*. There can also be secondary colonization by mold. Risk factors include wearing occlusive footwear and being immunocompromised.

Table 6 Treatment of tinea pedis

Agents	**Options**	
Dressings	Burow's wet dressing	Daily until resolution (typically over 2 weeks)
	Castellani paint	Daily until resolution (typically over 2 weeks)
	Aluminum chloride hexahydrate 20%	BID in chronic cases
Best topical agents	Terbinafine (Lamisil)	1% cream
	Butenafine (Lotrimin Ultra)	1% cream
Other topical agents	Imidazoles	Clotrimazole Miconazole Ketoconazole Econazole Oxiconazole Sertaconazole
	Allylamine	Naftifine
	Naphthenates	Tolnaftate
	Substituted pyridone	Ciclopirox olamine
Best oral agent regimens	**Agent**	**Dose**
	Fluconazole	150–200 mg/day for 4–6 weeks
	Itraconazole	Either 100 mg/day for 2 weeks or 200 mg/day for 1 week
	Terbinafine	250 mg/day for 2 weeks
	Griseofulvin	250 mg TID for 2 weeks

Body Distribution

Most commonly affects the nail of the big toe. Feet are affected 80% of the time.

Symptoms

Typically presents as asymptomatic color change in the nails. Can present with bacterial superinfection that would cause pain, erythema, and tenderness.

Diagnosis

Diagnosis cannot be made by clinical exam alone but requires fungal culture or dermatopathology.

- Fungal cultures: Can be done in KOH preparation with nail clipping.
- Dermatopathology: Fungus can be identified using periodic acid-Schiff or methenamine silver stain. Both are more sensitive than KOH preparation for this infection.

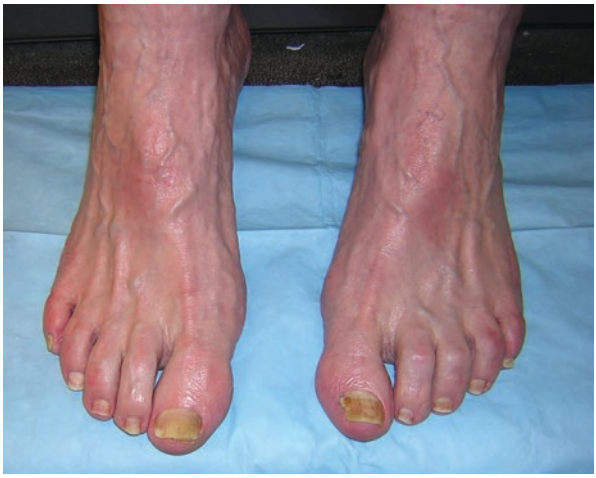

Fig. 8 Onychomycosis. Discoloration of nails on both toes. Tinea unguium (129_tine_ungu_hr). (Jefferson Clinical Images Database [4])

Description

Typically begins with a white patch that is noted at the edge of the nail. As the infection progresses, the nail can become completely discolored and become eroded from the nail bed allowing for easy removal (Fig. 8).

Differential

This can be mistaken for yellow nail syndrome, systemic amyloidosis, psoriasis vulgaris, onycholysis, onychauxis, and acral lentiginous melanoma.

Treatment

Treatment includes debridement and topical and systemic agents. Topical agents include ciclopirox nail lacquer which is only successful with concurrent debridement. Systemic treatments are listed below. Of note, the nails will not regain their normal appearance until well after treatment has been completed due to their slow growth (Table 7) [1, 2].

Table 7 Treatment of onychomycosis

Agent	Adult dose
Terbinafine	250 mg/day for 6 weeks for fingernails and 12–16 weeks for toenails
Itraconazole	200 mg/day for 6 weeks for fingernails and 12 weeks for toenails
Fluconazole	150–400 mg given once a week or 100–200 mg daily until the nails grow back normally
Ketoconazole	Not recommended given hepatotoxicity

Conclusions

Tinea infections are a common disease seen by primary care physicians. It is important to be able to identify tinea infections and treat appropriately. Use of KOH prep and Wood's lamps is a cost-effective way to differentiate tinea infections from bacterial infections. Always educate patients on the high transmission rates and decreasing risk factors such as contact with fomites and infected individuals and soils.

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Scabies and Head Lice

Alexis Sweeney, John J. Russell, and Erin Russell

Introduction

Scabies, the debilitating, itching disease caused by the mite, *S. scabiei*, has antagonized the human population for centuries. Harking back to medieval times, Italian writer and the "Father of Humanism," Francesco Petrarca (1304–1374), described his symptoms of scabies to colleague and kindred writer, Giovanni Boccaccio. In 1365, at 61 years old, Petrarca wrote, "I do not know how long it will torment me, an ugly and dry scabies, which is troublesome at all ages, but it is also dangerous at our age. Since five months, this illness oppresses me so much that the hands are prevented to use the pen and to take the food, but they serve only to scratch and scrape it I certainly know only one thing about my illness, that it will soon leave me or I will leave it: we cannot be together for a long time." [1]

As Petrarca described, scabies is detrimental to the elderly and immunocompromised, and its primary symptom is an intensive and "oppressive itch." In effect, the scratching can result in bacterial infections of the skin, such as impetigo caused by *S. aureus* and *S. pyogenes* [2]. More grisly complications may also result, including skin abscesses, cellulitis, and even necrotizing fasciitis, septicemia, renal disease, and rheumatic heart disease [3, 4].

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In addition, scabies can also take on a more severe form called crusted scabies, where the skin becomes hyperkeratotic and is resistant to treatment [5]. This is more typical in patients who are immunosuppressed, including those with HIV and diabetes, the elderly, and those who are malnourished or are taking chronic immunosuppressants [4]. Despite several effective treatment options, scabies continues to be a global issue due to its high rate of reinfection [6].

Etiology

Scabies is an infestation of the skin caused by the mite *Sarcoptes scabiei* (Fig. 1) which burrows under the skin and is transmitted through close personal contact, particularly in cases of overcrowding and poor personal hygiene or during sexual contact [7]. The mites enter the skin, burrow into the epidermis, and then reproduce [8] (Fig. 2). In size, female mites can measure up to 0.4 mm in length, while the

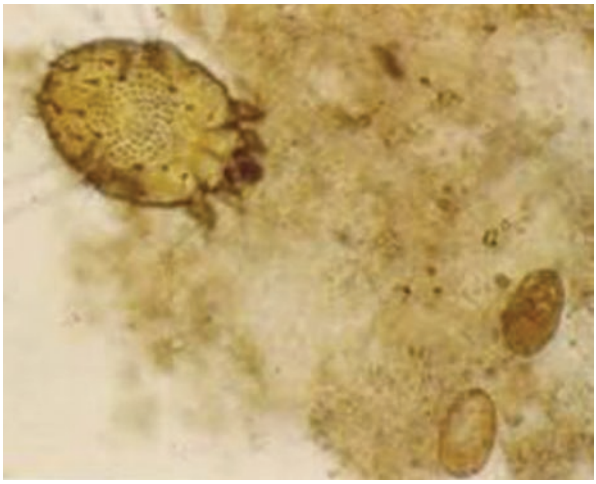

Fig. 1 *Sarcoptes scabiei*. (Photo on CDC.gov)

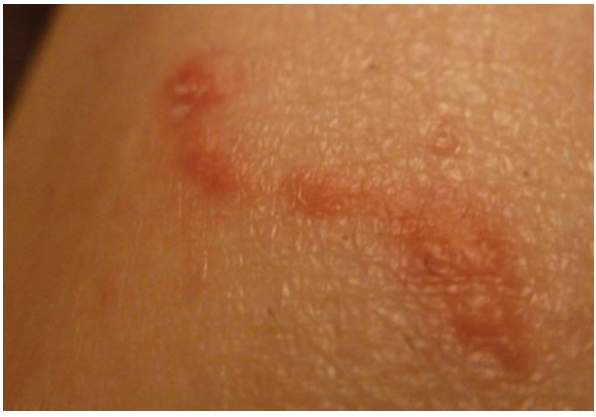

Fig. 2 Burrows. (Scabiespics.com)

male is much smaller and dies shortly after coition [7]. The skin then develops a delayed hypersensitivity reaction caused by the mites and their excreted contents. This reaction causes the characteristic scabies rash and extreme pruritus [8]. Transmission is predominantly via prolonged skin-to-skin contact and most commonly occurs between members of the same household [9].

Epidemiology

Scabies is most common in areas where there is overcrowding, limited access to water, and poor hygiene/lack of cleansing. Immunocompromised persons are especially predisposed to infestation and have particularly high mite counts. These include patients with HIV/AIDS, children, and the elderly with poor mobilization [5].

Globally, scabies primarily affects tropical islands of the Pacific. Other highly prevalent areas include Panama, Brazil, and Indigenous communities of Australia. In these locations, resources are sparse and few new health efforts can be initiated. In October 2013, the World Health Organization listed scabies as a neglected tropical disease. In addition, there have been few international health programs to assist with the population control of this infection [6]. However, with the establishment of the International Alliance for the Control of Scabies, interest and advocacy is promising [3].

Description of Rash and Body Distribution

The two most common manifestations of scabies are the classical form and the more precarious form of crusted scabies (also known as Norwegian scabies). Classically, a scabies rash is described as papular or vesicular lesions where the mites entered the skin and burrowed [10]. The appearance of symptoms is delayed until 4 weeks following initial contact [9] and can be intensely pruritic, especially at night [8]. The most common sites of infections include skin folds and flexor surfaces. In adults, infestation sites are typically in the interdigital web spaces, on the wrists (Figs. 3, 4, and 5), in the axillae, around the umbilicus, and in the groin or the popliteal fossa [8]. In older populations, the rash can appear as a diffuse truncal eruption. In younger populations, like infants and children, scabies may affect the face, scalp, palms, and soles [5].

In turn, crusted scabies (Fig. 6) is life-threatening and poorly understood. It is seen in the immunocompromised population and described as a proliferation of thousands of mites per gram of skin, leading to hyperkeratosis. Thickened skin crusts often form in the classical anatomic locations of skin folds and flexor surfaces, but they may also develop along the face, ears, and scalp. This form is resistant to treatment, leading to recurrent episodes of crusted scabies and causing significant depigmentation [10].

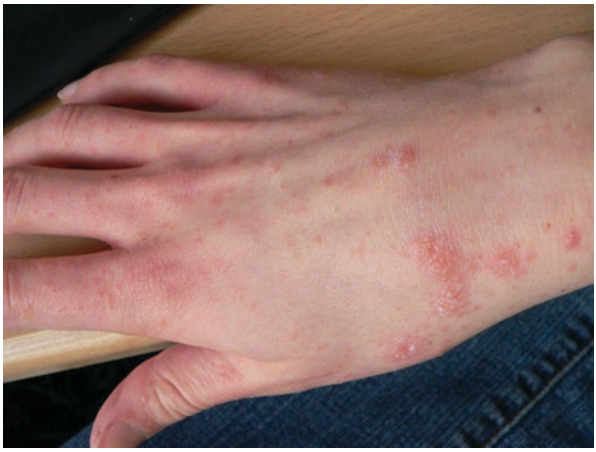

Fig. 3 Scabies. (Scabiespics.com)

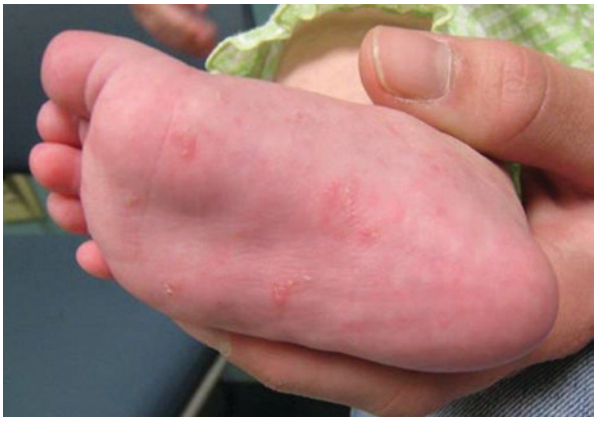

Fig. 4 Scabies foot. (Scabiespics.com)

In addition, there also appears to be a substantial psychological burden of the disease. In a 2012 study conducted in Brazil, 77.2% of adults with scabies reported feelings of shame, isolation, and stigmatization. Furthermore, the degree of social impairment correlated directly with the severity of infestation [11].

Treatment

There are various topical therapies utilized in the treatment of scabies. In a Cochrane review, permethrin 5% cream was found to be the most effective topical therapy (superior to lindane and crotamiton) [11]. Lindane should probably not be used any more for both efficacy and safety issues. Other topical therapies that have been used but have poorly studied effectiveness include benzyl benzoate, malathion, and sulfur compounds [5]. However, topical treatments often have poor adherence because of itching and high cost and can be laborious to apply [12]. In tropical locations where scabies is most common, topical therapies are even less well-tolerated due to the humidity [13].

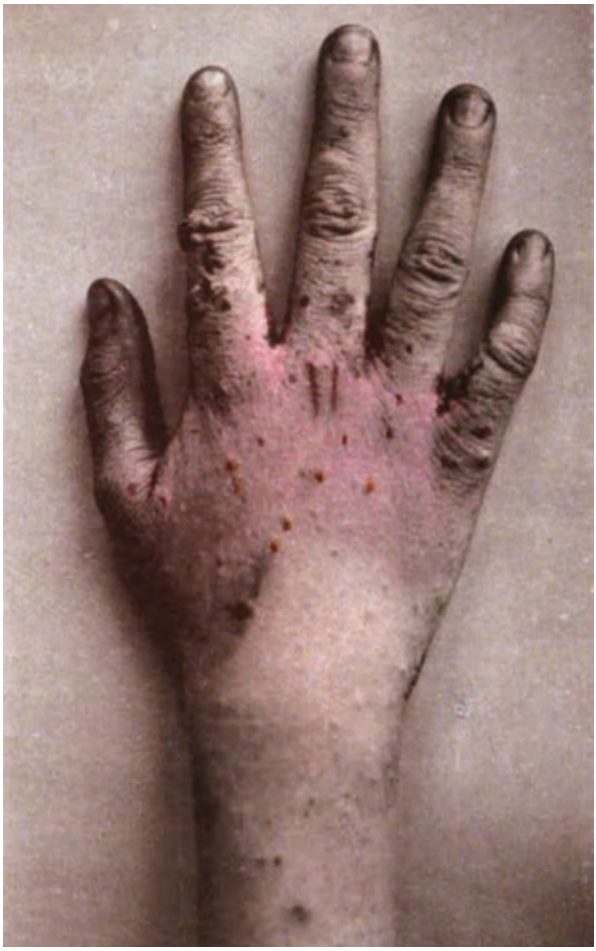

Fig. 5 Chronic scabies. (Fox [28], public domain)

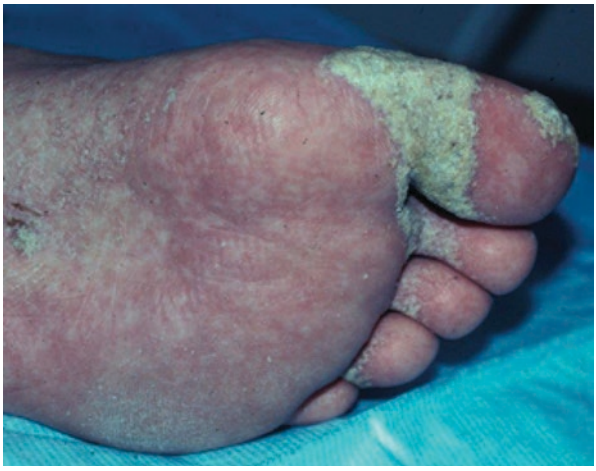

Fig. 6 Crusted scabies. (Scabiespics.com)

Permethrin 5% cream is applied as a one-time dose from hairline to toe and left on and rinsed off in the morning (8–14 hours later). Permethrin can be used in children over 2 months of age. Children under 2 months might be treated with a sulfur product.

Ivermectin, an oral therapy, is also showing more utility as previously, it was only reserved for cases refractory to topical treatment [3]. In a Cochrane review, ivermectin's effectiveness has been shown to be superior to placebo. However, topical permethrin was found to be superior to oral ivermectin [11]. Overall, ivermectin appears to be well-tolerated, but it is not yet licensed for scabies treatment in most countries [5]. There is also limited research that examines its safety and tolerability in infants [14].

The treatment of patients' household members is also standard to prevent reinfection and transmission. This is the recommended approach to patients with scabies; however, there is limited data to fully support this strategy [3].

Crusted scabies treatment is treated uniquely because of its high resistance to therapy [8]. A combination of topical permethrin and oral ivermectin has been shown to be effective. Keratolytic agents can also be applied to the hyperkeratotic crusts to improve the topical treatment's effectiveness [6, 15]. However at this time, there are no randomized control trials that directly compare and contrast treatment strategies for crusted scabies [8].

Head Lice

Epidemiology

Pediculus humanus capitis (Fig. 7), more commonly referred to as head lice, is a parasite found primarily on the human scalp and at times on the eyebrows and eyelashes. This disorder has been around for ages, being found in Egyptian mummies. In the United States, head lice are most commonly seen among children in

Fig. 7 *Pediculus humanus capitis*. (WikiCommons)

preschool and elementary school, as well as among their caregivers and household members. The presence of head lice is not related to a person's cleanliness or to the cleanliness of the environment they work or reside in. Though these parasites are not known to directly transmit disease, a secondary bacterial infection can develop due to scratching of the scalp.

The transmission of head lice from host to host is primarily attributed to direct contact with the hair of an infested person. Among children, this most commonly occurs at school, at home, or in other places where close contact is prominent (sporting events, playgrounds, camps, slumber parties). Other forms of transmission are possible but less common. This includes sharing clothes such as hats, scarves, coats, sports uniforms, or ribbons with an infested person. With that, using infested combs, brushes, and towels is a less common yet possible cause of transmission, in addition to lying on a bed, couch, pillow, carpet, or stuffed animal that was recently in contact with an infested person. Head lice cannot fly or hop, they can only crawl from person to person. Humans are the only suitable hosts for these parasites; dogs, cats, and other pets do not play a role in transmission.

Though there is no reliable data on the exact number of cases in the United States, it is estimated that about 6–12 million cases of head lice are seen nationally each year among children aged 3–11. Some studies suggest that girls contract head lice more often than boys, which is likely due to greater exposure to situations in which head-to-head contact is prevalent. In the United States, African Americans are less likely to acquire head lice than people of other races. The louse found most frequently in the United States may have claws that are better adapted to a particular type of hair shape and width and that are less efficient in other types of hair [16].

Life Cycle

There are three main stages in the life cycle of the *Pediculus humanus capitis*: egg, nymph, and adult (Figs. 8 and 9). Egg: The egg of a head louse is referred to as a "nit." These nits are oval shaped (0.8 mm by 0.3 mm in dimension) and are yellow

Fig. 8 Electron microscopy of head lice. (Photo on CDC.gov)

Fig. 9 Size perspective head lice. (Photo on CDC.gov)

Fig. 10 Close up of nit. (WikiCommons)

to white in color (Fig. 10). Nits are laid by adult females at the base of the hair shaft near the scalp. To be considered viable, nits must be within 6 mm of the scalp. Otherwise, the egg may have already hatched, may be empty, or may be non-viable. Nits typically hatch within 6–9 days.

Nymph: A nymph emerges from a nit upon hatching, and the nit shell becomes more visible to the eye, dull yellow in color. The nymph, roughly the size of a pinhead, becomes an adult after approximately 7–12 days, molting three times during this period. Adult: About the size of a sesame seed, an adult louse has six legs with claws on each. Their color ranges from a tan to grayish-white, appearing darker in persons with darker hair. Adult females are larger than adult males and are responsible for laying eggs. Females can lay about 6–8 nits per day and can live up to 30 days. However, without access to their food source (human blood), a louse will die within 1–2 days [17].

Clinical Presentation

Pediculosis is the most prevalent parasitic infestation among humans. Head lice infestations are pervasive among school-age children in the United States; ~6–12 million infestations occur each year in children 3–11 years of age [18]. The disorder

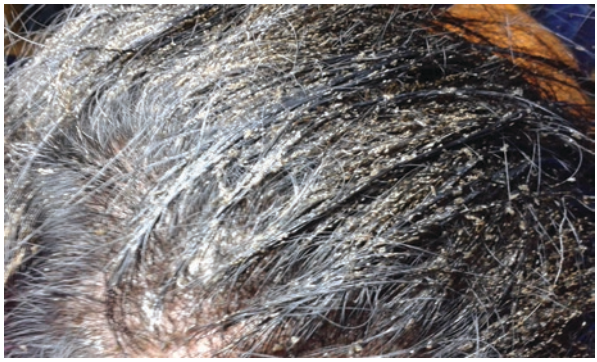

Fig. 11 Nits. (By Aditya Suseno—own work, CC0, https://commons.wikimedia.org/w/index.php?curid=32004712)

is more common in females. All socioeconomic groups are affected, [16, 19] and contrary to myth, "head lice prefer clean, healthyhosts." [20] Unlike many diseases, this diagnosis is often made at home. The presence of a live louse in a patient's (usually a child) hair is fairly straightforward. The majority of the time a diagnosis is made by a parent or a school nurse and treatment begins without contact with their physician. The bigger clinical issue occurs when the lice do not respond to treatment. The issue of nits (Fig. 11) can be problematic. Many schools have a "no-nit" policy to return to school. The American Academy of Pediatrics (AAP) and National Association of School Nurses do not think that children should be excluded from school for the presence of nits [19, 21]. A nit that is greater than 1 cm from the scalp is likely to be nonviable [16]. Also the diagnosis of head lice is more problematic and can often be confused with other illness like seborrheic dermatitis [20].

The symptoms of head lice include itching of the scalp. These symptoms might not appear until later in the infestation period. Chronic infestation can lead to redness of the scalp (Fig. 12).

Treatment

After a diagnosis is made, the clinician should discuss treatment options with the patient (or their parents). The oldest treatment available is the physical removal of nits. This is where the term "nit-picking" is derived. In a patient with a lot of hair, this can be a long and arduous process. There are special nit combs that can help with this task. In some communities, there are some hair salons that will help do this but often at considerable cost. Often the physical removal of nits follows treatment. Nit removal can be aided by applying a 50% vinegar solution after treatment with a topical product. Use of hair conditioner may make this easier as well. Treatment should be based on patient needs and should include efficacy, safety, and convenience and should take into account local resistance patterns and whether the product will kill the unhatched eggs which is termed being "ovicidal."

Most patients start the treatment process with pyrethrin or permethrin shampoos. Pyrethrins are derived from chrysanthemums and have been used safely for years.

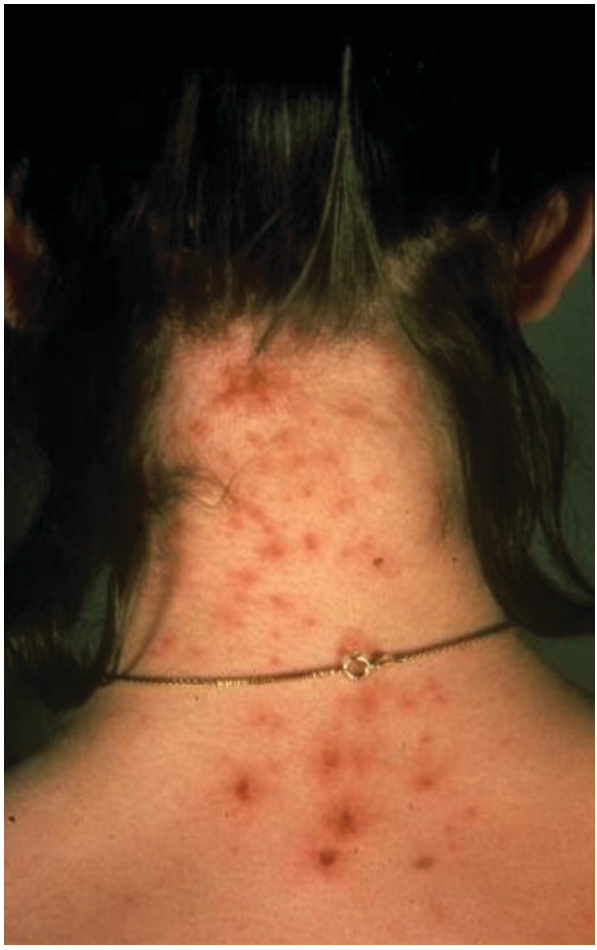

Fig. 12 Chronic head lice changes. (WikiCommons—KostaMumcuoglu)

Permethrin is a synthetic compound based on pyrethrins. These products are placed in the hair and left in place for a period of time before rinsing them out. This is followed by combing out the nits. These products are available over the counter and are affordable for families. Both of these classes of products are not ovicidal and need to be reapplied in a week. Issues of resistance have emerged surrounding these products with resistance patterns in some cities in the United States as high as 75% [22].

Another product that has been used for years is lindane. This topical product probably should be used with great caution. There have been questions raised about the safety of this product with regard to the nervous systems of children, and there are questions about diminishing efficacy [23].

Malathion had been removed from the market in the United States and has recently been returned to use. This prescription product is topically applied to hair. Studies have found the efficacy of this product around 98%. It is partially ovicidal and sometimes needs reapplication. Safety issues have arisen about high alcohol

content of this product and caution about flammability in using with blow dryers [23]. The product is also malodorous and can cause some local stinging.

Topical ivermectin is a product that a 5% formulation of the oral product mentioned in the scabies section. This product works quickly on live lice. It is not ovicidal per se but the eggs that hatch are unable to feed and die off. The product does not need reapplication or 100% removal of nits. This product has a reported efficacy of 74% at 15 days and is well-tolerated but is several hundred dollars for a course of treatment [24].

Topical benzyl alcohol is a product that looks to suffocate the lice. This is based on historical treatments with petrolatum or mayonnaise left in place. The issue with these historical treatments was that the lice had an ability to close off their respiratory spiracles. This could lead to a "Lazarus-like" awakening of these lice and a failure of these physical methods. The 5% benzyl alcohol uses a thick vehicle, but the product holds the respiratory spiracles open and suffocates the louse. Studies have found 75% efficacy at 2 weeks. This product is very safe and effective. Because of its mechanism, one should not expect resistance to develop. The product is expensive and available by prescription [23].

Spinosad is a semisynthetic product derived from a soil actinomycete. It causes paralysis and death in insects. It appears to be ovicidal. It contains 10% benzyl alcohol. It has been found to have an efficacy of 85–87% at 2 weeks. It can cause some scalp irritation [23].

Off-label treatment includes oral treatment with trimethoprim/sulfamethoxazole. This medication kills the essential bacterial flora that resides in the stomach of the louse. The clinician should weight the risks and benefits of this common oral antibiotic [25]. Oral ivermectin is only approved for onchocerciasis and strongyloidiasis, but a dose of 400 mcg/kg has been found to be about 95% effective for head lice in a trial versus malathion [26]. Ivermectin will need a repeat course in 7–10 days to kill any hatched nymphs.

Recommended Topical Mediations for Head Lice

	Brand name	Directions	Advantages	Disadvantages
Permethrin	NIX	Apply to recently washed hair, towel dried hair, leave on for 10 minutes, repeat in 7–10 days	Cost, availability	Resistance, not ovicidal
Pyrethrins	RID	Apply to dry hair for 10 minutes, rinse, repeat in 7–10 days	Cost, availability	Resistance, not ovicidal

(continued)

(continued)

	Brand name	Directions	Advantages	Disadvantages
Malathion	Ovide	Apply to dry hair, rinse in 8–12 hours	Efficacy	Flammable with blow dryer, not for use under 6 years of age, malodorous, only partially ovicidal, cost
Topical ivermectin	Sklice	Apply to dry hair and scalp then rinse	Efficacy, single treatment, no resistance reported	Cost
Benzyl alcohol 5%	Ulesfia	Apply to dry hair, rinse in 10 minutes, repeat in 7 days	Efficacy, no resistance reported	Cost, not ovicidal
Spinosad 0.9% suspension	Natroba	Apply to dry hair, rinse in 10 minutes, repeat in 7 days as needed	Efficacy, no resistance reported	Cost, scalp irritation

Treating the Environment

In reality, this is a disease with very little morbidity and no mortality but has great emotional consequence for afflicted families. We should recognize this and help educate families on how to decrease reinfection. The louse cannot live off a human host after several hours. We can recommend patients to wash bedding and personal items in hot water with heated drying in washing machine and dryer. Products that are unable to be cleaned that way can be sealed in a plastic bag for 2 weeks. Brushes and combs should be washed in hot water for 10 minutes. Spraying pediculicides on furniture is not necessary [27].

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Common Nail Disorders

Jennifer Thuener

Nail disorders are commonly seen in the primary care office and can frequently be seen every day if being looked for. Nail disorders can range from benign curiosities to malignant tumors and frequently have a broad differential diagnosis. The astute clinician should be aware of these conditions and look for them in their practice. Three common maladies are discussed below.

Onychomycosis

Onychomycosis is a very common nail disease frequently seen in the primary care office and is considered the most commonly occurring nail disorder in adults [1]. Overall, it is reported that onychomycosis accounts for 15–40% of all nail diseases [2]. Onychomycosis affects patients worldwide [2]. Risk factors for onychomycosis include older age, peripheral vascular disease (PVD), trauma, and diabetes [2].

Onychomycosis is a general term that refers to infection of the nail from either dermatophyte, yeast, or non-dermatophyte mold infections. Toenail onychomycosis is generally caused by dermatophytes, as up to 82% of cases in the United States were caused by dermatophytes [3].

Diagnosis of onychomycosis is generally made on physical findings (Figs. 1 and 2). However, it is essential to confirm the diagnosis with accepted confirmatory laboratory testing, either a KOH prep or a fungal culture, as many nail disorders can mimic the clinical findings of onychomycosis [4]. Another option is sending off nail clippings for a PAS stain. If clinical suspicion is high but initial laboratory findings

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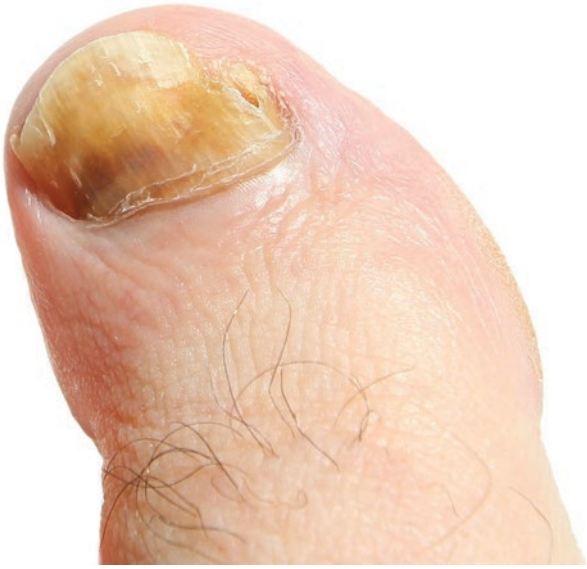

Fig. 1 Onychomycosis. (By Lionel Allorge—own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=33429544)

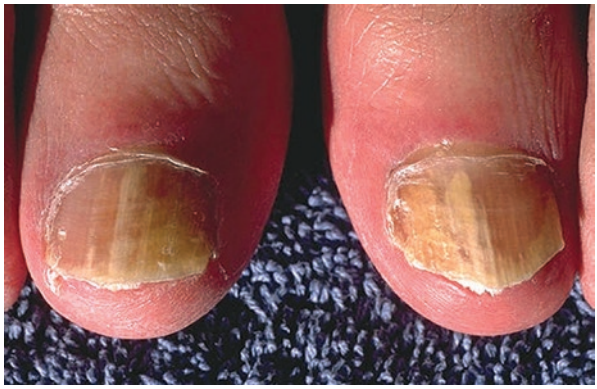

Fig. 2 Onychomycosis. (CDC)

are negative, then laboratory testing should be repeated [4]. Onychomycosis should not be treated without laboratory confirmation of fungal infection. Clinical presentation varies on subtype of infection, the two most common subtypes being distal and lateral subungual onychomycosis (DLSO) and superficial white onychomycosis (SWO). DLSO is the most common presentation of a dermatophyte infection. The fungal infection enters the nail at the distal and lateral margins, and the nail will present as thickened and discolored and may present with some separation of the nail from the nail bed [2]. The infection in SWO begins at the superficial layer of the nail plate and spreads deeper. This presents as a dry, white, powdering appearance of the nail, with the nail still adhered to the nail bed [2].

Treatment of onychomycosis is usually considered to be for cosmetic reasons alone; however, providers need to explore if there is any associated discomfort and

difficulty walking or finding appropriate footwear. In patients with immunocompromise or diabetes, it is important to treat this infection, as the disruption of the integrity of the skin can lead to cellulitis, osteomyelitis, and foot ulcers [2].

Setting goals and expectations of appearance of the nail post treatment is important for patient satisfaction in management of this disease. Most patients seeking treatment for onychomycosis are hoping for a normal appearing nail. Patients should be informed that it can take 12–18 months for the toenail to grow completely out and be replaced with healthy, treated nail. Patients should not expect the appearance of the toenail to improve until this time can pass. Even despite adequate therapy and growth of non-infected nail, there can still be an unusual appearance to the nail, which is unrelated to fungal infection [4].

Treatment for superficial infections or early DLSO, which is defined as <80% of the nail plate affected, can include topical medications as monotherapy. Topical therapies include amorolfine, ciclopirox, tavaborole, and tioconazole. Cure rates are lower than systemic therapies, but there is currently no strong evidence that one topical therapy is better than another [4]. A small pilot study demonstrated clinical improvement of onychomycosis with over-the-counter mentholated ointment, with a positive effect in 83% of patients [5]. Given the low cost and lack of side effects, this may be a consideration for many patients, pending more investigations and further research. For infections that do not meet the criteria for topical monotherapy, systemic therapy is indicated. Terbinafine is considered first-line systemic therapy, with cure rates of 76% [6]. Hepatic toxicity can occur, but it is rare. Patients with active or chronic liver disease should not receive this medication. If there is any history of heavy alcohol use, liver disease, or hematologic abnormalities, it is recommended that patients have LFTs and a CBC prior to therapy [4]. For patients in which terbinafine would not be recommended, itraconazole can be used [2].

Onychomycosis is a common physical finding, but the visual presentation is different with each type of onychomycosis, and this can easily be confused with other nail disorders. The three most common nail disorders that can be confused with onychomycosis are psoriatic nail disease (Fig. 3), nail trauma, and lichen planus. Psoriatic nail disease can present in many ways, but frequently causes the nail to separate from the nail bed (onycholysis) (Fig. 4) and causes accumulation

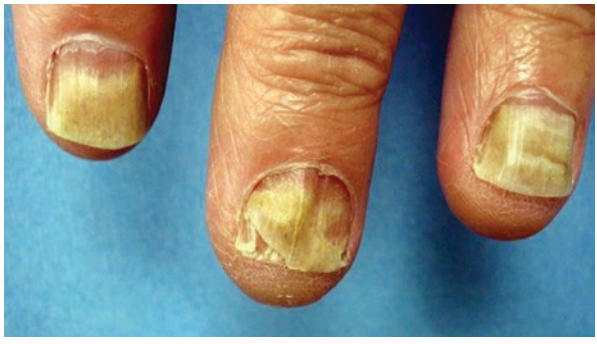

Fig. 3 Nails with pitting and onycholysis from psoriasis. (With permission of James Studdiford, MD/ Thomas Jefferson University)

Fig. 4 Onycholysis. (With permission of Alborz Fallah, https://commons.wikimedia.org)

of yellow, scaly debris under the nail and yellowing of the nail, all of which are very similar in appearance to onychomycosis. Psoriatic nails can present with pitting of the nails, which, if present, can distinguish it from onychomycosis. Nail trauma can also cause onycholysis, and the area of the nail that is nonadherent to the nail bed appears white, yellow, or green toned. This can be similar in appearance to onychomycosis and should be considered in the differential when one encounters white nails. Lichen planus of the nail bed can appear as longitudinal ridges and grooves in the nail, inflammation of the matrix, and splitting of the nails. These can be clinically confused with onychomycosis, which is why it is essential to test with a fungal culture prior to diagnosis and treatment of onychomycosis.

Onycholysis

Acute and Chronic Paronychia

Paronychia is an infection of the tissue immediately surrounding the nail tissues [7]. Acute paronychia is generally the result of minor trauma to the nail bed, which can be related to nail biting, finger sucking, or ingrown nails (Fig. 5). *Staphylococcus aureus* is frequently the infectious cause; however, herpes simplex should also be considered [7, 8]. Acute paronychia often presents with pain, erythema, and inflammation of the nail folds, generally limited to a single digit.

Management can be conservative, such as warm soaks and topical antibiotics. However, if there is a localized, purulent area along the proximal or lateral edges of

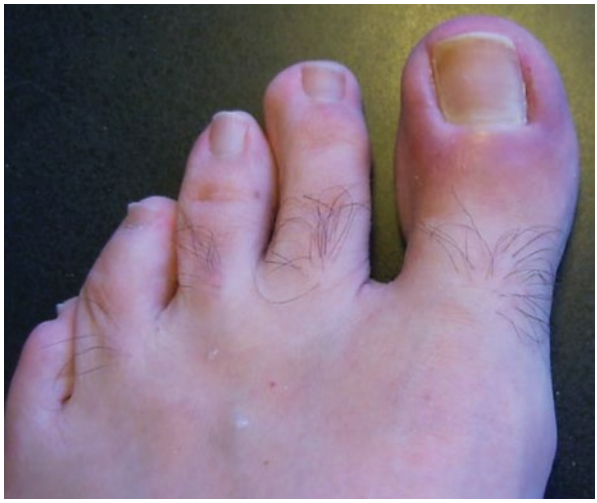

Fig. 5 Paronychia. (By User: DocEss—own work by the original uploader, public domain https://commons.wikimedia.org/w/index.php?curid=53698529)

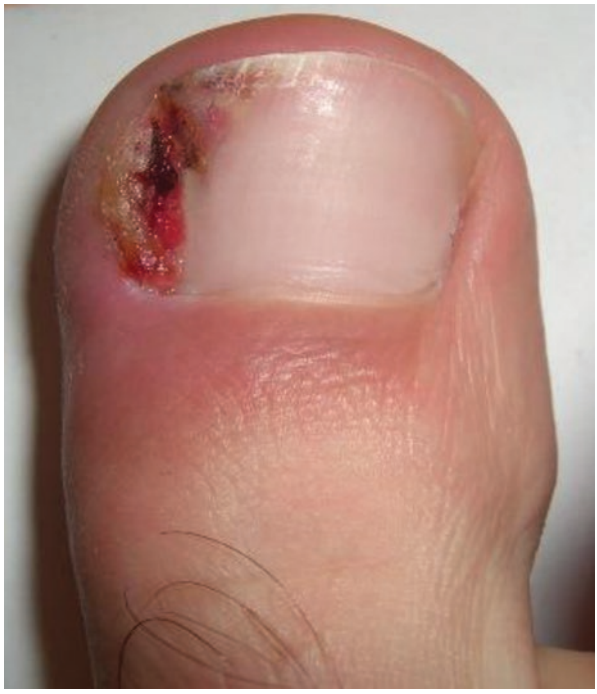

Fig. 6 Paronychia. (WikiCommons)

the nail, then in-office surgical management is needed (Fig. 6). A simple nick with an 11 blade through the most translucent area of the abscess should suffice [9].

Chronic paronychia is diagnosed when the patient has had pain and erythema near the nail folds for at least 6 weeks. Chronic paronychia is most commonly seen in the thumb and second and third fingers of the dominant hand and, unlike acute

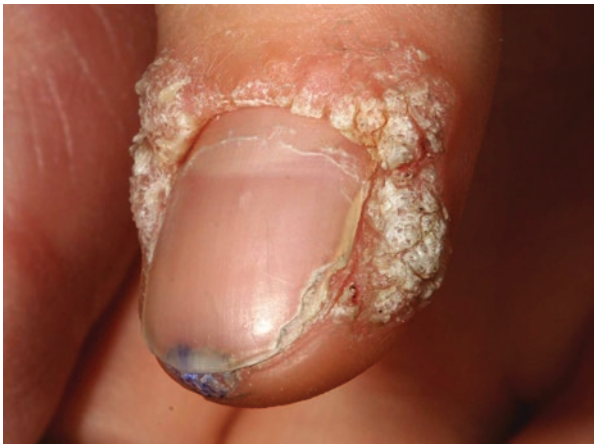

Fig. 7 Periungual warts. (DermNet NZ—Dr Raimo Suhonen)

paronychia, may be seen in more than one digit [8]. Chronic paronychia is not felt to be secondary to bacterial infection but rather to inflammation of the nail fold due to repeated trauma. It is often seen in patients that have repeated and prolonged exposure to water, such as laundry workers, house and office cleaners, food handlers, cooks, dishwashers, bartenders, chefs, nurses, and swimmers [8, 10]. *Candida* or gram-positive organisms are frequently cultured from the tissue; however, it is felt that this is colonization following the inflammation, not the causative agent of the inflammation [10].

Treatment of chronic paronychia (Fig. 7) is the removal or avoidance of the offending inflammatory cause. High-potency topical steroids and a topical antifungal agent will assist in decreasing inflammation and treatment of colonized *Candida* [10]. Patients should avoid trimming cuticles and irritants to the cuticles and avoid excessive exposure to water.

Growths

Periungual warts are the most common growth of the nail and surrounding tissue [10]. Warts can either occur beneath the nail which are described as subungual or surrounding the nail, described as periungual (Fig. 7). The causative agent is human papillomavirus, which enters the skin through any break in the skin barrier. The development of warts can occur anywhere from a few weeks to greater than 1 year following exposure to the virus [11]. Warts in children will usually resolve without intervention, so no treatment is acceptable and preferred [12]. For adults, first-line treatment is salicylic acid. This agent is applied topically daily for 4–6 weeks [12]. Other topical agents that can be considered include imiquimod, podophyllotoxin, glutaraldehyde, or compounded cidofovir [12]. Cryotherapy can be considered but was found to have no improved clearance at 12 weeks and 6 months over topical therapy and was less cost effective [11].

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Psoriasis

Seyed Parham Khalili

Introduction

Psoriasis is a relatively common disease among pediatric and adult populations worldwide. Given its chronic and clinically unpredictable course, psoriasis has been shown to decrease quality of life roughly on par with chronic cardiovascular disease, diabetes, renal disease, and even cancer [1]. Moreover psoriasis has been shown to have a tremendous economic impact which correlates with disease severity, such that the costs of care for individuals with even moderate psoriasis may be nearly twice as high as the general population when considering direct medical care and medication expenditures [2]. Primary care physicians may be among the first clinicians sought out by patients with signs and symptoms of this disease and are in a position to not only diagnose this condition but to also initiate high-quality patient-centered treatment, and assist in the coordination of care for individuals with ambiguous, refractory, or severe disease.

Epidemiology and Pathophysiology

The 2016 World Health Organization's report on psoriasis summarizes the volume of epidemiological research on psoriasis prevalence worldwide, highlighting a range of 0.9% to 11.4% [3, 4]. Among children and adolescents with psoriasis in the United States and Germany, the incidence has most recently been estimated to be 40.8/100,000 person-years with a median age of onset between 7 and 10 years, and

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it may be increasing over time [5, 6]. With respect to adults in the United States, one systematic review suggested an incidence rate of 78.9/100,000 person-years and prevalence of 0.91%, while a more recent study estimated a prevalence of 3.2%, with higher occurrence among Caucasians than other racial groups [7, 8]. Prior epidemiologic studies of adult patients suggested a possible bimodal pattern of disease with one cohort exhibiting systems prior to age 30 and a second, larger group presenting between 50 and 60 years of age [9].

While there have been numerous studies exploring the underlying autoimmune mechanism(s) for the development of psoriasis, the precise genetic architecture of the disease remains somewhat unclear. More than 40 susceptibility loci, particular regions of the genome, have been identified as likely to be associated with epigenetic and environmental exposures culminating in phenotypic disease. Specific facets of the immunologic and inflammatory process include infiltration by T cells and dendritic cells which produce cytokines including tumor necrosis factor α (TNFα), interferon γ (IFNγ), interleukins (IL-17, IL-22, IL-23, IL-1β), neutrophil collections in the epidermis, and increased vascularity through angiogenic factors [10–12].

There appear to be important differences in pathophysiology across psoriasis subtype. Specifically, guttate psoriasis appears to be a distinct entity as it generally arises in children and young adults and seems to display a strong genetic link [13, 14]. Further, the pathophysiology of both chronic plaque and guttate psoriasis may involve "Th1 and Th17 cells, innate immune cells, and regulatory T cells" and, as was mentioned earlier, a cascade of inflammatory cytokines [15, 16]. Relatedly stressors such as recent upper respiratory tract streptococcal infection are often noted 1–3 weeks prior to the appearance of skin lesions, and such "triggering infections" may be as much as nine times more common in guttate psoriasis compared to other subtypes [17]. Contemporary theories on the link point to potential cross-reactivity between streptococcal antigens and epidermis [18]. A 2016 systematic review and meta-analysis on *Staphylococcus aureus* carriage in several chronic cutaneous conditions suggested that colonization by this organism may be increasing and contributory to the chronic inflammation [19].

Symptoms and Diagnosis

Subtypes of Psoriasis

In general psoriasis is diagnosed based on clinical presentation after a careful history and physical exam. Psoriasis subtypes, as discussed in greater detail below, include plaque, guttate, nail, pustular, inverse, and erythrodermic. Skin biopsy and/or early referral to a dermatologist is warranted where the presentation is not "classic" or if the condition does not improve with treatment.

Formally known in the research literature as psoriasis vulgaris, plaque psoriasis is the most common and most commonly studied subtype, making up 85–90% of patients with this disease [20]. Characteristic exam findings include papules and

plaques usually located over extensor surfaces (knees, elbows) (Fig. 1) but may also involve the scalp (Fig. 2), neck, trunk and back, groin, and distal extremities. These skin lesions are usually well-demarcated, feature a silver scale, and bleed when unroofed (a positive Auspitz's sign). In addition some patients may report that the lesions arose in an area of prior skin trauma (Koebner's phenomenon).

Guttate psoriasis is usually characterized by the relatively acute onset of scattered sub-1 cm erythematous, monomorphic teardrop-shaped macules or papules ("gutta") over the trunk and limbs (Fig. 3), either occurring in isolation (acute guttate psoriasis) or as part of the clinical trajectory of chronic plaque psoriasis. If the diagnosis is unclear, a skin biopsy may be obtained for histological examination, and diagnostic findings would include hyperkeratosis, parakeratosis, neutrophils in the stratum corneum, and potentially also dilated capillaries in the dermis [13]. An acute flare generally resolves over the course of weeks to months but as many as 30–60% of individuals may subsequently progress to chronic psoriasis, though

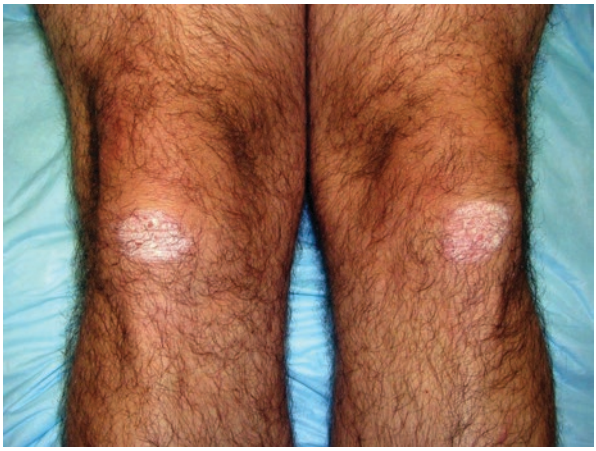

Fig. 1 Plaque psoriasis. (used with permission from James Studdiford, MD/Thomas Jefferson University)

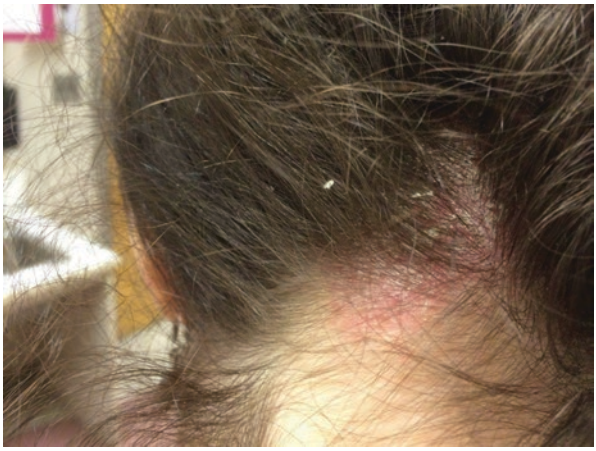

Fig. 2 Scalp psoriasis. (used with permission from James Studdiford, MD/Thomas Jefferson University)

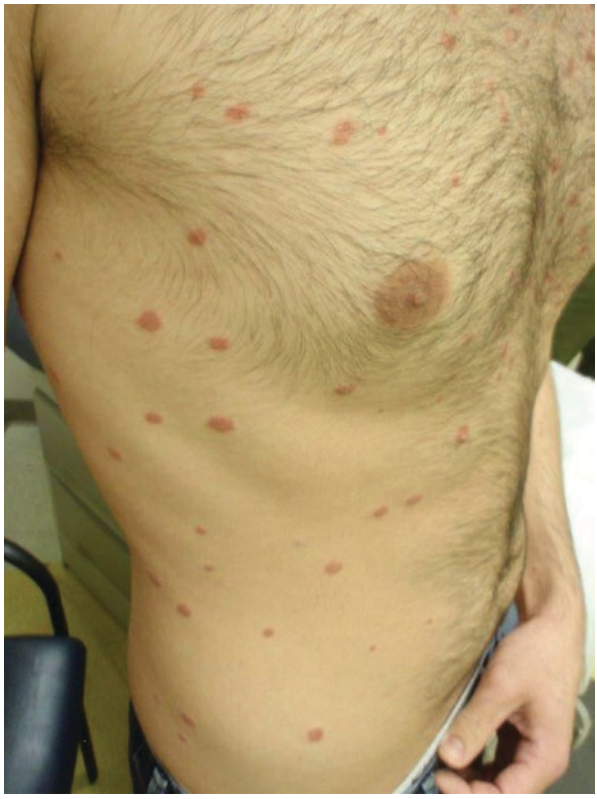

Fig. 3 Guttate psoriasis. (used with permission from James Studdiford, MD/Thomas Jefferson University)

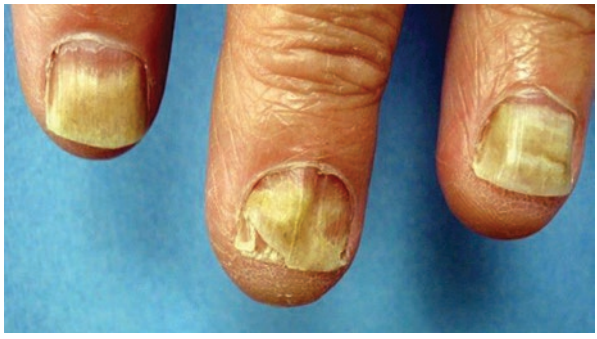

Fig. 4 Nail psoriasis. (used with permission from James Studdiford, MD/Thomas Jefferson University)

there is limited long-term data on younger individuals. Associated potential triggers may include recent streptococcal infection, as well as use and/or sudden cessation of use of various categories of systemic medications [21].

The lifetime incidence of nail psoriasis may be as high as 80–90% among patients with plaque psoriasis and in general may be underreported in the literature among patients with any type of psoriasis [22–25]. While nail psoriasis may occur in the absence of skin and joint manifestations, its presence may be a predictor of future psoriatic arthritis [26]. The clinical presentation of nail psoriasis (Fig. 4) may be

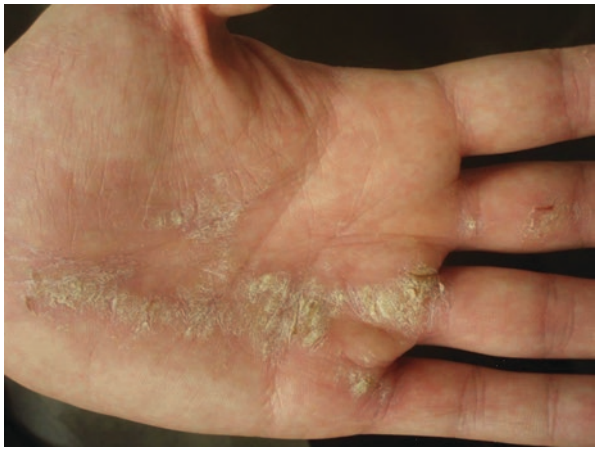

Fig. 5 Pustular psoriasis. (used with permission from James Studdiford, MD/Thomas Jefferson University)

nonspecific in some cases and in general varies according to whether the nail matrix, nail bed, or periungual region is affected. The nail matrix may feature pitting, leukonychia, red spots on the lunula, or Beau's lines (transverse grooves), while the nail bed may demonstrate oil-drop discoloration, splinter hemorrhages, hyperkeratosis under the nail, and even onycholysis [25]. Clinical distinction between the site of predominant involvement informs subsequent decision-making on therapeutic options.

Pustular psoriasis (Fig. 5) may present commonly as palmar or plantar lesions or rarely as generalized disease though it may also be closely associated with psoriatic arthritis. Lesions appear as sterile pustules or vesicles that may be painful or pruritic and may arise de novo or within prior skin lesions (e.g., plaques) or sites of cutaneous trauma (Koebner phenomenon here as well).

Inverse psoriasis manifests in intertriginous regions including the inguinal and intergluteal skin folds, below the breast, in the axillae, and potentially along the neck. These lesions are often painful, well-demarcated erythematous plaques and papules. Given the location of the rash, the skin may become secondarily damaged by friction and subsequent contamination by skin pathogens. Given the nature of this variant's appearance, it may be confused with cutaneous candidiasis or erythrasma, and it will fail to improve with topical antifungal or antibiotic regimens (barring a secondary infection).

Erythrodermic psoriasis is a rare subtype that may manifest acutely or chronically and varies dramatically in severity and care needs. Severe flares may be precipitated by a variety of factors including medications, stress, and systemic infections to name a few. Acutely it presents over several days as diffuse erythema affecting often over 75% of total body surface area, often with edema (Fig. 6), exfoliation, hair loss, and nail dystrophy, and it may be life threatening due to electrolyte abnormalities and multi-organ strain (e.g., high-output heart failure) from the severe systemic inflammatory state [26]. The diagnosis is usually based on the overall patient presentation and any salient personal or family history though skin biopsy may be helpful when there is uncertainty.

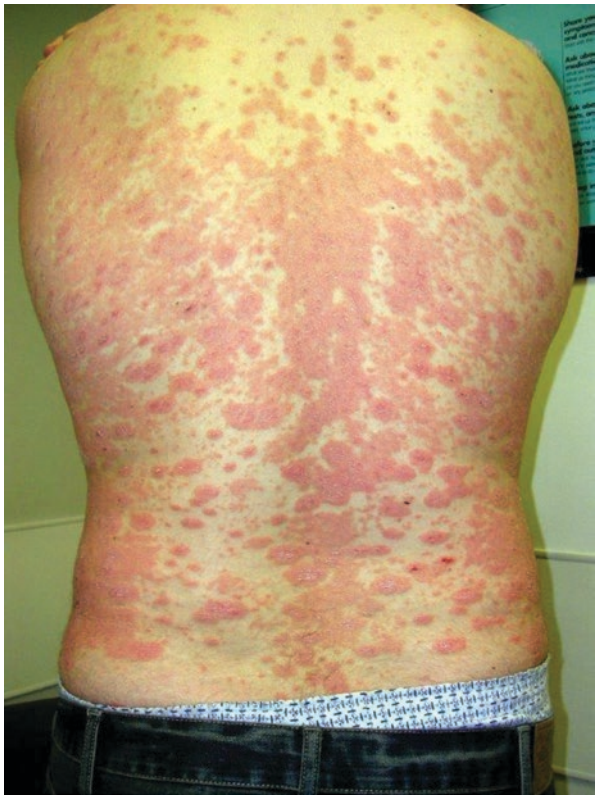

Fig. 6 Erythrodermic psoriasis. (used with permission from James Studdiford, MD/Thomas Jefferson University)

Disease Severity

Across subtype, disease severity may be estimated in several ways. The total percentage of affected body surface area (BSA) remains a useful guide and may be readily estimated during the clinical encounter. The clinician may use the patient's own palmar handprint as a measurement tool, such that in general each handprint would represent 0.8% of total BSA for men, 0.7% for women, and 0.94% for children [27, 28]. In general, aggregate percent BSA categories of less than 5%, between 5% and 10%, and over 10% may represent mild, moderate-to-severe, and severe disease, respectively [29]. In addition involvement of certain areas of the body, such as the periorbital region or the palms and soles, may pose particular challenges and also elevate the global estimation of severity.

In addition to the rough estimation of affected BSA, there are over a dozen published formal scales for categorizing the severity of disease. One of the most commonly cited instruments is the Psoriasis Area and Severity Index (PASI), and it provides a mechanism for delineating mild, moderate, and severe disease. Calculators for this instrument are available online, and combine estimates of severity (erythema, induration, and desquamation) with percentage of BSA for the head,

trunk, arms, and legs [30]. A PASI score below 7 indicates mild disease, a score of 7–12 implies moderate disease, and a score above 12 strongly suggests severe disease though it is notable that severe disease and disease that severely affects quality of life are distinct entities to be teased apart by the treating clinician. The strengths of the PASI scoring system include its history as a validated instrument, now ubiquitous use in clinical trials ("gold standard"), high correlation with objective outcome measures, and ease of use, while limitations include the lack of a clear correlation to quality of life measures and patients' views on their disease, the lack of a *linear* relationship to cutaneous disease severity, and lack of applicability in measuring disease course over time [31].

Non-dermatologic Manifestations and Closely Associated Conditions

While an in-depth discussion is beyond the scope of this chapter, psoriatic arthritis (PsA) is a common concomitant condition to consider during the evaluation and treatment of patients with cutaneous disease (Fig. 7). Itself a heterogeneous disease

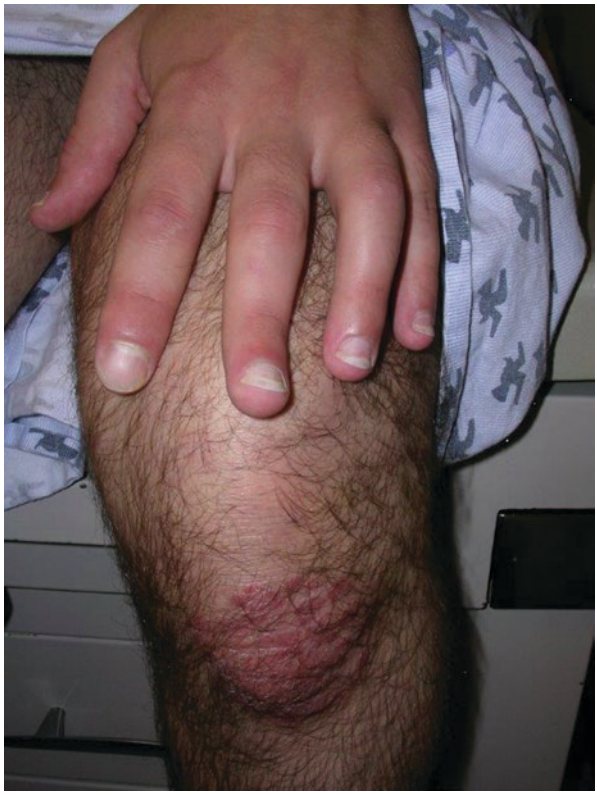

Fig. 7 Psoriatic arthritis. (used with permission from James Studdiford, MD/Thomas Jefferson University)

entity, PsA mirrors seronegative spondyloarthropathies based on clinical and genetic features, and it is estimated that up to 40% of patients with psoriasis will develop PsA within 10 years of the onset of skin disease [32]. Some studies have estimated the prevalence of *undiagnosed* disease as between 10.1% and 15.5%, suggesting that clinicians should consider actively screening psoriasis patients for the presence of peripheral inflammatory pain, axial inflammatory pain, dactylitis, and buttock-sciatic pain to improve detection [33, 34]. Fewer patients may present to the primary care provider with signs or symptoms of arthropathy first, though since this may be the case in as many as 10–15% of patients, clinicians should remain vigilant in an individual with a strong family history [35]. Though not initially developed to diagnose PsA, the Classification Criteria for Psoriatic Arthritis (CASPAR) tool remains useful and has demonstrated 99% specificity for classifying PsA. A total score of 3 or higher is considered positive, and scoring is based on clinical criteria; the patient must have established inflammatory articular disease (joint, spine, entheseal). Points are allotted as follows: current diagnosis of psoriasis [2 points], history of psoriasis in the patient or his/her family [1 point], presence of dactylitis on exam or in the past [1 point], psoriatic nail dystrophy on exam [1 point]), radiographic criteria (juxta-articular new-bone formation [1 point]), and serological testing (Rh factor negative [1 point]) [36].

A growing body of literature highlights the association, if not causal link, between psoriasis and other systemic chronic conditions and exposures, which may be of particular interest to primary care providers. Specifically psoriasis appears to be associated with metabolic syndrome, obesity, alcohol use, tobacco use, COPD, significantly increased risk for adverse cardiovascular events and incidence of diabetes mellitus, and potentially some types of malignancies (e.g., non-Hodgkin's lymphoma, non-melanoma skin cancers) [37–45]. Patients presenting for assessment of possible psoriasis may thereby potentially benefit from screening for these other conditions.

Treatment

Non-systemic Therapy for Adult Patients

Most evaluations of treatment options for cutaneous psoriasis have focused on plaque psoriasis, and so there is more limited data on the effectiveness of the various topical and systemic regimens on other variants. Furthermore, decision-making around which individual modality or combination of therapies is complex in that clinicians and patients need to engage in a careful discussion of the strength of the existing effectiveness data, patient preferences, side-effect tolerability, practical logistics (e.g., dosing frequency), and cost.

The American Academy of Dermatology Work Group published guidelines for the management of psoriasis and psoriatic arthritis in 2011, providing insight regarding treatment approaches for mild, moderate, and severe disease. The workgroup suggests that in general first-line therapy for cutaneous manifestations of chronic

mild psoriasis includes topical corticosteroids, vitamin D analogues (calcipotriol, calcipotriene, calcitriol; inhibit keratinocyte proliferation and enhance differentiation), combination topical steroid-topical calcipotriene, and a topical calcineurin inhibitor (tacrolimus). In regard to psoriasis of the genital area, author Meeuwis and colleagues recommend an algorithmic approach, starting with mild topical corticosteroids, progressing to moderate potency topical corticosteroids, then using a calcineurin inhibitor cream as monotherapy or in combination with a mild topical corticosteroid, and lastly considering coal tar cream [46]. Secondarily used agents generally include tar-based preparations as well as dithranol, salicylic acid, and vitamin A products (e.g., tazarotene, a retinoid). Long advocated, coal tar appears to be potentially therapeutic and cost-effective in the treatment of mild to moderate psoriasis, but its use is limited by side effects such as odor and staining [47]. A 2013 Cochrane intervention review of 177 randomized controlled trials suggested that vitamin D analogues were superior to placebo and coal tar but not necessarily dithranol, and that they were associated with more skin irritation and possibly less robust improvement compared to steroids [48]. With regard to chronic plaque psoriasis, a systematic review by Hendriks and colleagues suggested that a two-compound therapy consisting of potent corticosteroids with calcipotriol could be effective in as little as 2 weeks and was not inferior to combinations with tazarotene or calcineurin inhibitors [49]. An even more recent systematic review of interventions specifically for scalp psoriasis examined 59 randomized controlled trials and suggested that topical corticosteroids of various potency, moderate to very high, performed similarly while two-agent combination regimens including steroids and vitamin D analogues may be slightly more effective than monotherapy with either agent, though research on performance beyond 6–12 months is still needed [50]. Of note, all topical psoriasis medications are labeled pregnancy category C except for tazarotene which is category X.

Phototherapy represents yet another tool for treatment, particularly for individuals with disease which is larger in anatomic scope (>5% BSA) and/or refractory to topical agents. Systematic reviews and meta-analyses have been performed on a heterogeneous body of literature with mixed findings. A 2013 Cochrane review examining narrowband ultraviolet B (NB-UVB) compared to broadband ultraviolet B (BB-UVB) or psoralen-ultraviolet A (PUVA) found differences in effectiveness across subtype of psoriasis, such that these modalities are specifically similarly effective for chronic plaque and guttate psoriasis but NB-UVB is probably ineffective for palmopustular psoriasis [51]. A more recent systematic review and meta-analysis reported however that PUVA appeared to be more effective than targeted UVB or photodynamic therapy (PDT) for chronic plaque psoriasis including palmoplantar disease [52]. In addition, 2016 guidelines from the British Association of Dermatologists and British Photodermatology Group suggest that treatment with PUVA is generally indicated for chronic plaque psoriasis if NB-UVB has not been effective, given the latter is simpler and leads to fewer side effects [53]. Phototherapy may be combined with topical or systemic agents. Patients with significant palmoplantar (pustular) psoriasis, as a notable example, may particularly benefit from phototherapy combined with low-dose systemic agents and topical corticosteroids under occlusion [54].

With regard to nail psoriasis, patients should be informed about the slow rate of improvement with most therapies, with some modalities requiring up to 1 year for maximum effect. Topical treatment is well suited to the majority of individuals, particularly if disease is limited to mild nail involvement. Non-systemic treatment options include corticosteroids (topical or intralesional), vitamin D3 derivatives (calcipotriol, tacalcitol, calcitriol), tazarotene, calcineurin inhibitors, anthralin, 5-fluorouracil, allopurinol, intralesional methotrexate, colloidal silicic acid, and indigo naturalis extract [27]. Those with more severe nail involvement and those with comorbid psoriatic arthritis, severe cutaneous disease, and/or significantly lowered quality of life may be candidates for systemic therapy.

Systemic Therapies for Adult Patients

According to numerous sources, including the American Academy of Dermatology Work Group, systemic therapy, similar to phototherapy, is reserved for individuals with diffuse (>5% BSA) or more severe disease (including usually and especially erythrodermic psoriasis). Historically, oral systemic agents have included methotrexate (MTX), cyclosporine, and acitretin. MTX is the most frequently employed medication for moderate-to-severe psoriasis across the world and is an agent with which many clinicians have significant experience. Clinically there have been concerns about the use of MTX and development of liver fibrosis though a 2014 systematic review failed to demonstrate a clear association between cumulative dose and this complication [55]. The use of MTX requires serious consideration of risk of pregnancy (category X agent), monitoring of blood counts and liver enzymes, and patient tolerance of side effects such as nausea and fatigue [56]. Cyclosporine's use is limited by nephrotoxicity in particular, and it is approved in the United States for only up to 1 year of continuous therapy, thereby chiefly relegating it to duty as a "rescue" agent [57]. Acitretin is an oral retinoid which may be used as monotherapy or in combination with phototherapy, though its use is limited by dose-dependent mucocutaneous side effects and elevations in liver enzymes and triglycerides; in addition it is contraindicated in women of childbearing potential.

Other agents for consideration include fumaric acid esters (FAEs) and antibiotics. FAEs have been an option for systemic therapy though until recently there have been few comprehensive analyses of their efficacy or long-term safety. A recently updated Cochrane systematic review of six studies on oral fumaric acid esters (FAEs) suggested that existing evidence quality is low-very low, that FAE may be similar in efficacy to methotrexate and superior to placebo, and that several "nuisance" side effects such as gastrointestinal discomfort and flushing may limit tolerability [58]. Similarly a separate systematic review by Balak et al. reviewed 37 observational studies and 7 heterogeneous randomized controlled trials, finding a significant (42–65%) reduction in PASI scores after 12–16 weeks of treatment but limited tolerability due to the aforementioned side effects, as well as case reports describing multifocal leukoencephalopathy and Fanconi syndrome [59]. Future studies examining long-term benefits and risks are needed. While there is no formal

recommendation to use antibacterial agents in the management of guttate or chronic plaque psoriasis, and a 2010 Cochrane review found no clear evidence of benefit from acute or prophylactic use of antistreptococcal antibiotics or tonsillectomy, an updated Cochrane review is underway. [60, 61]

Newer systemic therapies consist of biologic agents and small molecule inhibitors that target specific inflammatory pathways. Preliminary evidence suggests that these agents may be more appropriate for patients with multiple comorbidities and on multiple medications, feature no obvious salient drug-drug interactions, and do not necessarily appear to cause statistically significant increases in serious adverse effects (e.g., cardiovascular events, malignancy). [57, 62–64] TNF inhibitors consist of adalimumab (human monoclonal antibody against TNFα), etanercept (human immunoglobulin G1 fused with the p75 receptor), certolizumab (PEGylated FAB' fragment of a humanized TNF inhibitor monoclonal antibody), golimumab (a novel monoclonal antibody against TNFα), and infliximab (monoclonal antibody against TNFα). T cell modulators include abatacept (a protein that inhibits T cell signaling and activation), itolizumab (humanized IgG1 monoclonal antibody which targets a marker involved with T cell stimulation and maturation), and alefacept (fusion protein of a portion of human leucocyte function antigen-3 with human IgG1) now that efalizumab has been withdrawn. The category of phosphodiesterase 4 inhibitors includes a lone agent, apremilast (increases cAMP leading to lower levels of inflammatory cytokines). Interleukin inhibition agents include ustekinumab (monoclonal antibody against p40 subunit of IL12 and IL23), brodalumab (monoclonal antibody against interleukin receptors for IL17A, IL17F, and IL23), ixekizumab (humanized monoclonal IL17A antibody), secukinumab (IL17A monoclonal antibody), and tocilizumab (monoclonal antibody against IL6). Finally, B cell depletion therapy consists of rituximab (monoclonal antibody against the CD20 protein).

Anti-TNF agents are commonly first-line among the newer systemic therapies [57]. A 2016 systematic review of infliximab suggested improvement in clinical course and quality of life with the most common adverse events or symptoms consisting of pain, hepatic dysfunction, and infusion site complications [65]. It has been suggested that patients with psoriasis and psoriatic arthritis are first treated with a single anti-TNF agent, however, given a paucity of clinical and cost-effectiveness studies to date, the optimal second-line agent for those who fail to respond to the initial therapy is less clear [62, 66]. A 2016 systematic review of the efficacy of switching to a second TNF inhibitor after failure of the first reported week 24 response rates ranging from 30% to 74% for a 75% reduction in the PASI score, with a wide range in rates of adverse effects, suggesting that some patients may potentially benefit from a trial of a second TNF inhibitor [67].

A 2014 systematic review by Busard et al. examined various combination regimens: more than one traditional systemic agent, phototherapy with traditional systemic agents, phototherapy with biologics, and biologics with traditional systemic agents; the authors found moderate support for acitretin/calcitriol, etretinate/eicosapentaenoic acid, betamethasone/methotrexate, UVB/methotrexate and PUVA/methotrexate, UVB/ustekinumab, and etanercept/methotrexate [68]. The authors of that analysis also point out the clear need for additional research before reliable guidelines may be advocated due to the heterogeneous strength of evidence on effectiveness and long-term safety of these regimens. A recent review of phase III clinical

trial data on anti-IL17 agents, secukinumab, ixekizumab, and brodalumab, suggests that within 12 weeks of treatment all three agents led to a greater than 75% improvement in PASI scores and shared similar mild adverse effect profiles [69].

Complementary Therapies

There is an emerging body of literature examining complementary and alternative medicine, including therapies such as acupuncture, herbal therapies and dietary supplements, mindfulness interventions, and traditional Chinese medicine to name a few. To date, there remain mixed findings overall, as most studies are hampered by small sample sizes, significant confounding bias, and a lack of long-term follow-up. In addition there remain concerns about tolerability and side effects [70]. A thorough discussion of the risks and benefits of these therapeutic options is encouraged with patients who express interest.

Treatment for Pediatric Patients

In general, management of pediatric psoriasis should explicitly include shared decision-making with the patient and his/her family. The decision regarding treatment regimen may be informed by factors such as age, comorbidities and treatment history, disease severity, and impact on quality of life [71]. Most children have mild or moderate disease and do not require systemic therapies. A systematic review of systemic treatments for children and adolescents with more severe psoriasis found that the level of evidence (LOE; Oxford Centre for Evidence-Based Medicine) was grade C for MTX, cyclosporine, retinoids, and FAEs, while it was grade A for etanercept based on efficacy and safety data (up to 96 weeks for the latter agent) [72]. A 2015 Cochrane review limited to anti-TNF agents for pediatric psoriasis based its recommendations in part on a study of 211 participants and determined that etanercept tentatively did appear to be efficacious and safe in the short term [73]. Unfortunately since there are no standardized guidelines for systemic management of pediatric psoriasis, ultimately clinicians must generally base shared decision-making with pediatric patients and their families on guidelines for adult psoriasis, the limited number of pediatric psoriasis studies and review articles, expert opinions, and studies of drugs utilized in other pediatric conditions [71, 74].

The Role of Patient Preferences

As noted above there are a variety of treatment options and approaches for the management of psoriatic disease. While there is a growing body of literature on the various pharmacologic agents described, there is a paucity of work eliciting and

incorporating patient preferences though there is evidence that such preferences are measurable and, based on studies on other chronic diseases, play an important role in both the patient experience and clinical outcomes [74]. Primary care providers should strongly consider employing a shared decision-making approach to treatment regimen design and monitoring.

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Diagnostic Evaluation Using Biopsy and Dermoscopy

Mathew Clark

The primary care evaluation and treatment of skin disorders presents the practitioner with multiple situations in which a dermatologic procedure might be helpful. Some of these procedures are easy to learn and perform, with little risk of adverse consequences. Others require more time and experience to master and have more associated risks. This chapter reviews common dermatologic procedures, with the goal of helping the practitioner to become more familiar with their indications, limitations, and performance. It is anticipated that practitioners who are unfamiliar with a particular procedure will make use of available mentors and resources in order to become comfortable making it part of their clinical practice.

Dermoscopy

Dermoscopy—traditionally a diagnostic technique which was limited to dermatologists—is increasingly finding a place in primary care. This reflects the availability of smaller, more affordable instruments, and more widespread training in this helpful diagnostic tool.

A dermoscope provides a magnified (typically 10×), illuminated, polarized view of skin lesions in vivo, allowing the examiner to gain valuable information without the necessity of first performing a biopsy or excision. In the evaluation of pigmented lesions, dermoscopic examination may be sufficiently reassuring that biopsy is deemed inappropriate. Alternatively, a lesion that initially appears benign may show concerning dermoscopic features and lead to a decision to biopsy. Dermoscopy can

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be useful in diagnosing seborrheic keratosis, dermatofibroma, and other benign skin neoplasms. Dermoscopy can also be very helpful in identifying features that are characteristic of basal cell or squamous cell carcinoma and in differentiating benign pigmented lesions from lesions suspicious for malignant melanoma (Figs. 1 and 2).

Appropriate use of a dermoscope does involve a commitment of time and energy to become familiar with typical dermoscopic features of the skin lesions in question. This can occur with the use of self-directed learning materials or through a variety of focused educational activities available to primary care practitioners.

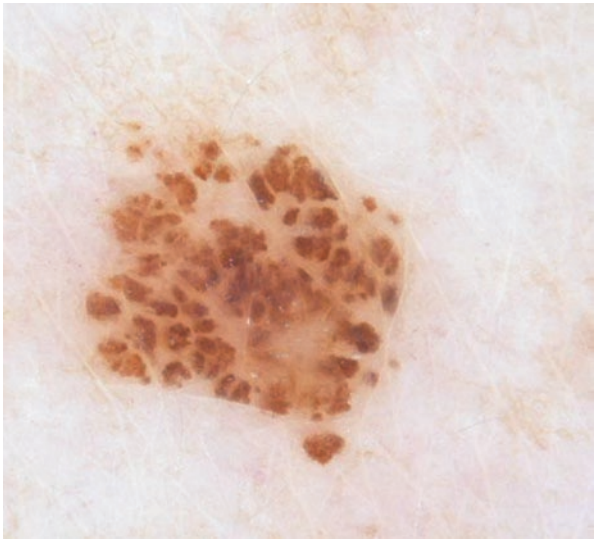

Fig. 1 Benign nevus under dermoscope. (Note homogeneous pattern; DermNet NZ)

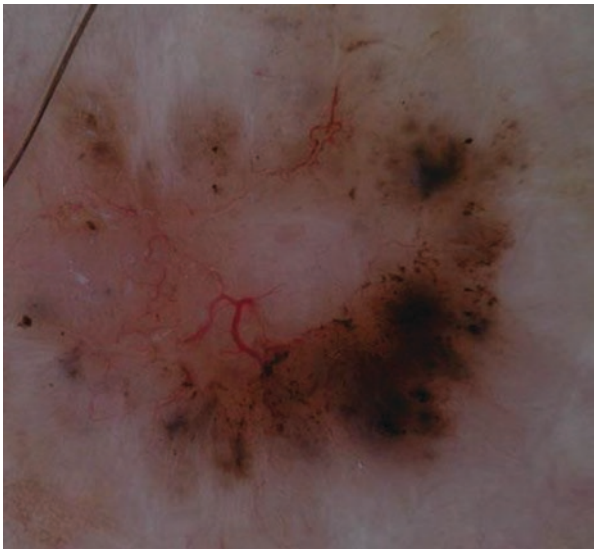

Fig. 2 Basal cell carcinoma under dermoscope. (Note blood vessels, uneven pigment; DermNet NZ)

The rewards, however, are considerable. Dermoscopy can greatly enhance the diagnostic capabilities in a primary care setting, helping to make subsequent procedures more appropriately performed. Many models also allow the practitioner to take digital photos through the dermoscope, often using the camera on a smart phone, and to use these images for documentation and communication with a specialist [1, 2].

Biopsy

There are many situations in which appropriate diagnosis and treatment of a skin lesion is aided by obtaining a biopsy specimen. Whether or not to biopsy, and which type of biopsy to use, depends on a variety of factors.

It is important to bear in mind that all biopsy techniques involve the likelihood of at least minimal scarring. Accordingly, biopsy should not be used as a substitute for diagnostic experience; if it is likely that an experienced dermatologist could identify a rash or lesion clinically, referral may be more appropriate than biopsy. Additionally, the use of dermoscopy may help to confirm the benign nature of a lesion, making a biopsy unnecessary. If a skin biopsy is indicated, one should seek to use the least invasive biopsy technique that is likely to result in an adequate diagnostic specimen. In some cases, this may involve a full-thickness elliptical excision—a surgical technique that is beyond the scope of this chapter.

The following biopsy techniques are appropriate for regular use in a primary care setting.

Punch Biopsy

Punch biopsy allows a practitioner to obtain a full-thickness dermatologic specimen, which can be sent to a lab for pathologic diagnosis. This can be used to identify a variety of skin neoplasms, characterize a rash, or—if the lesion is small enough and the biopsy instrument large enough—completely excise a lesion. Once learned, this technique can be quickly performed as part of a normal office visit, minimizing delay and inconvenience for the patient.

When doing a punch biopsy, it is important to remember that one is usually only obtaining a sample of a larger lesion. Accordingly, the practitioner needs to choose the biopsy site so that the specimen is representative of the entire lesion, and be aware that sampling errors may occur. A benign biopsy in an otherwise concerning lesion may require complete excision for definitive diagnosis. Dermoscopic examination prior to selecting the biopsy site may help in this respect.

Disposable biopsy punches come in a variety of sizes. A 2 mm specimen has the advantage of leaving a very small defect, which minimizes bleeding and visible scar. This usually provides enough tissue for an accurate histologic diagnosis. A

4 mm biopsy provides a larger sample, and allows the pathologist to see larger architectural patterns and structures, but leaves a larger defect, which may take longer to heal, with a more visible scar [3].

Technique

- Skin should be anesthetized with appropriate local anesthetic. Use of epinephrine-containing solution, and waiting a few minutes for optimal vasoconstriction, will help to minimize bleeding.
- The biopsy instrument is placed against the skin, and twirled back and forth between the fingers, while applying gentle downward pressure. This rotation is important and allows the instrument to cut through the skin, rather than attempting to simply force it through, as one might with a cookie-cutter.
- Your goal is to penetrate through the dermis, just entering the subcutaneous tissue. Deeper biopsies are unnecessary, and risk bleeding and injury of deeper structures. This appropriate depth can be judged by a combination of feel—one often notices a lack of resistance as the dermis is penetrated—and sight, as the cutting portion of the instrument disappears below the surface. One rarely wants to bury the instrument up to the barrel or handle.
- Once the cut is made, the biopsy instrument is withdrawn. The specimen is then gently lifted from its bed, by applying pressure on the surrounding skin with forceps, bringing the forceps together to grasp the specimen, raising the specimen slightly, and freeing the underlying tissue attachments by use of small scissors or scalpel.
- Hemostasis can be obtained with aluminum chloride, electro-cautery, or pressure.

In most cases, wounds are simply covered with gauze and a Band-Aid and allowed to close by themselves. Suture closure of biopsy defects of 4 mm or less is not necessary and in fact may lead to a less desirable cosmetic outcome, due to the resultant suture marks. Suturing or steristrips may be worthwhile with larger biopsies, or in areas of high skin tension [4].

Shave Biopsy

Many lesions can be removed or biopsied using a shave technique, in which a scalpel—typically a #15 blade—is moved parallel to the skin surface through the lesion, obtaining a flat slice. For some superficial lesions, such as seborrheic keratosis, a shave biopsy accomplishes two goals: a specimen is obtained for pathologic diagnosis, and the lesion is effectively removed.

Shave biopsy has two important limitations. First, it can be challenging to control the depth of your shave, leading to biopsies that are unnecessarily deep (with longer healing and increased scar) or too superficial (with portions of the lesion left behind). When an initial shave attempt is too shallow, it can be difficult to accurately remove the remaining lesion with subsequent passes of the scalpel. Practice and experience can minimize this problem.

A second limitation of shave biopsy involves the superficial depth of the specimen obtained. Since information about lesion depth and penetration is not obtainable with a shave biopsy, this important guide to therapy and prognosis would be lost after using this technique in a deep lesion. Accordingly, shave biopsy is inappropriate in pigmented lesions where malignant melanoma is a significant diagnostic possibility. Dermoscopic evaluation prior to biopsy may help the practitioner decide whether or not to use a shave technique on a particular lesion.

Technique

- Anesthetize the area around the lesion, using local anesthetic with epinephrine. A partially intradermal injection, creating a small wheal, is helpful in making the lesion more accessible to the blade.
- Using an even back-and-forth motion, the scalpel is advanced through the lesion, parallel to the skin surface.
- As the shave progresses, grasp the loose end of the lesion gently with forceps, applying counter traction, until the lesion is free.
- Hemostasis can be obtained as described above and the site covered with ointment and a Band-Aid.

Dermablade™

A modification of the shave technique, with some important advantages, involves the use of a Dermablade. This instrument is essentially a flat, flexible blade which is mounted in a plastic housing, allowing the operator to squeeze the ends together, creating an increasingly deep “U” shape (Fig. 3). By passing this blade through the lesion while simultaneously rocking the blade back and forth, one is able to obtain a specimen of variable depth in the center, which tapers off to the skin surface along the edges.

Unlike a traditional shave biopsy, a specimen obtained with a Dermablade can penetrate completely through the dermis to the subcutaneous fat, allowing for good information regarding lesion depth and architecture. Accordingly, this technique may be more appropriate for removal or biopsy of deeper or pigmented lesions, including nevi. On the other hand, scars that result from Dermablade excisions will

Fig. 3 Dermablade

tend to be more significant, which may limit the use of this technique in cosmetically sensitive areas.

Technique is similar to that described for a shave biopsy, although the "U" shape of the blade requires a somewhat different back-and-forth motion. There are several useful instructional videos available online to demonstrate appropriate Dermablade technique.

Cryotherapy

Many skin lesions can be treated by techniques that use extreme cold to destroy tissue. Appropriate lesions for this treatment modality include warts, actinic keratoses, and seborrheic keratoses [5].

There are several options for delivering cryotherapy. Liquid nitrogen, the cryogen of choice, is very cold—negative 196 °C—and quickly and effectively freezes tissue. Because it boils readily at room temperature, it must be stored in a heavily insulated tank, and used in small amounts, as needed. Liquid nitrogen will evaporate over time, even with minimal use, and therefore necessitates periodic tank refills. For this reason, it is probably most appropriate and financially viable for use in an office with multiple practitioners or in a practice with a strong dermatologic component.

Liquid nitrogen may be applied by partially filling a special hand-held thermos with an attached spray nozzle. Alternatively, the liquid can be dispensed into a Styrofoam cup and repeatedly dabbed onto the lesion, using a swab.

An alternative to liquid nitrogen involves purchasing a prefilled, pressurized can containing a refrigerant. A variety of such products are available, both for use by practitioners and over the counter. Some patients and practitioners report satisfactory results with these products, but they are significantly less cold—negative 50–80 °C. As such, tissue destruction is more variable, particularly for larger or thicker lesions.

Cryotherapy may be more difficult to titrate or control, compared to methods which employ physical destruction of a lesion. A freeze which is too superficial or brief will result in incomplete lesion treatment, while a freeze which is too aggressive may result in unnecessarily extensive tissue destruction, including full-thickness loss of surrounding skin.

Superficial lesions, including actinic keratoses, may be treated with a single freeze-thaw cycle, involving 4–5 seconds of lesion whitening. Deeper lesions, such as plantar warts, may respond more effectively to a longer, repeated freeze, after allowing the lesion to thaw for a minute or two. Freeze duration longer than 20 seconds may be associated with deeper tissue injury, risking necrosis and damage to underlying structures.

Electrodessication and Curettage

Curettage, combined with electrodessication, offers an effective method for destruction of a variety of common skin lesions, including actinic or seborrheic keratoses, cherry angiomata, and some basal cell carcinomas. Disposable dermal curettes, like disposable scalpels, offer the advantage of an inexpensive, sharp, and sterile instrument. While curettes come in a variety of sizes, 4 mm is a fairly versatile choice.

Use of a dermal curette helps to prevent an excessively deep excision, since—unlike a scalpel or Dermablade—a curette will not easily penetrate deep into healthy skin. This allows the practitioner to remove superficial lesions, such as seborrheic keratosis, while leaving the underlying skin relatively untouched. Curettage can be usefully combined with electrodessication. For example, applying light electrodessication to a seborrheic keratosis often allows the lesion to be easily removed with light pressure from a dermal curette, creating a very superficial wound that heals with minimal scarring.

Electrodessication and curettage is also useful for treating many basal cell carcinomas. A dermal curette will tend to delineate the extent of involvement with a basal cell carcinoma, since the healthy surrounding skin will resist the effects of the curette, while the soft, friable tissue of the lesion will not. Typically, three cycles of curettage and dessication are used for treatment of basal cell carcinoma, with good cosmetic results and low rates of recurrence.

Larger basal cell carcinomas, or lesions in cosmetically sensitive areas, are best treated with excisional techniques, including Mohs micrographic surgery [6].

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Benign Cutaneous Lesions

Harmony Bonnes and Mathew Clark

Primary care providers are frequently asked to identify skin lesions and recommend treatment. It is helpful to be familiar with some common, benign lesions so that we can distinguish them from more worrisome neoplasms and guide our patients in making informed treatment decisions. Many of these lesions can be effectively treated in our offices.

Seborrheic Keratosis

Seborrheic keratoses, the most common benign skin lesions, are also known as senile or seborrheic warts. They usually appear in middle life but can occur as early as adolescence. They occur equally in men and women [1]. While their exact cause is unknown, sun exposure [1] and genetics [2] have been implicated. These lesions are commonly found on the face, neck, trunk, or proximal extremities and usually spare the palms and soles. A seborrheic keratosis typically appears as a skin-toned to brown-black papule or plaque with sharply demarcated edges and exophytic, "stuck-on," often verrucous appearance; some have overlying scales (Fig. 1). On dermoscopy, they classically demonstrate "milia-like cysts, comedo-like openings, a gyrated surface, and looped vessels" [3] along with typical features of ridges,

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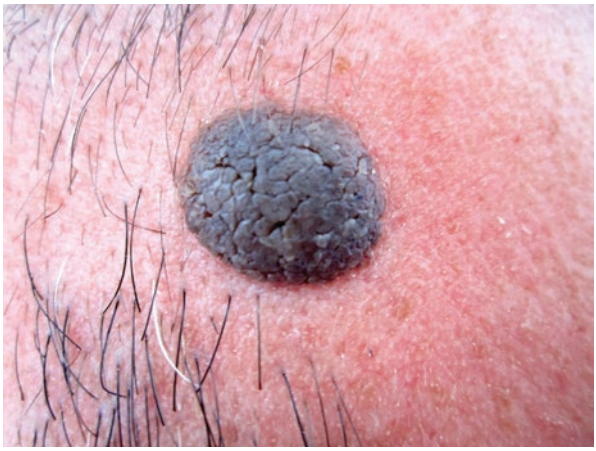

Fig. 1 Seborrheic keratosis. (WikiCommons)

furrows, and pseudocysts [4]. Biopsy may confirm the diagnosis when clinical examination and dermoscopy are equivocal.

Seborrheic keratoses are usually asymptomatic but may become pruritic or irritated. If a patient elects to have these lesions treated, options include cryotherapy, shaving, or electrodesiccation and curettage [5]. Surgical excision is not indicated, as these lesions are quite superficial. It is important to note the sign of Leser-Trélat, which is the sudden onset of multiple seborrheic keratoses in association with an underlying malignancy, the most common malignancy involving the gastrointestinal tract [6]. This sign warrants a full malignancy workup.

Acrochordons

Acrochordons, also known as skin tags or fibroepithelial polyps, are common cutaneous lesions. They typically begin to present in the second decade of life and continue to increase in frequency up until about the fifth decade. There is no gender predilection and 50% of all people will have at least one skin tag [7]. There is a familial predisposition, as well as an association to obesity, hyperlipidemia, hypertension, and insulin resistance, lending to the thought that skin tags may be a marker of increased risk for cardiovascular disease [8, 9]. There are also some studies that link skin tags to colonic polyps; however, more recent research does not support the correlation [10].

Acrochordons are predominantly located in skin folds such as the eyelid, neck, axilla, and groin but can occur on any cutaneous surface. They present as skin-toned to brown pedunculated papules usually a few millimeters in size but can reach diameters of several centimeters (Fig. 2). They are typically asymptomatic; however, they may become pruritic or irritated by catching on clothing or jewelry. The stalk can also become strangulated and the skin tag infarcted; this leads to a purple to

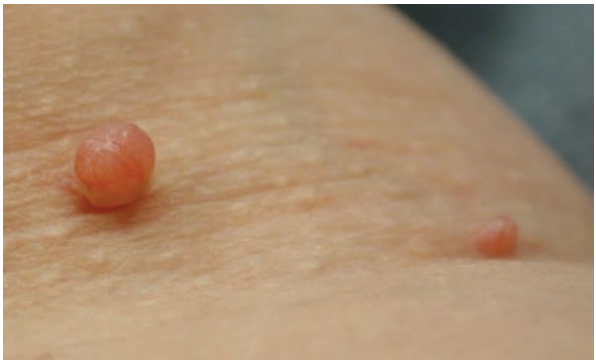

Fig. 2 Acrochordons. (WikiCommons)

black appearance and spontaneous avulsion. Skin tags are usually clinically diagnosed and do not require treatment, unless desired by the patient; however, any abnormality warrants a biopsy to differentiate from early nodular basal cell carcinoma [11]. Removal can be performed via scissor excision, shave biopsy, cryotherapy, or electrocautery and is usually curative [5]. These superficial lesions, when small, are most comfortably removed without injecting local anesthetic; such injection is reserved for lesions with a larger base.

Cherry Angiomas

Cherry angiomas are also known as Campbell de Morgan spots, cherry hemangiomas, or senile angiomas. They are the most common vascular malformation; they occur in almost all people in older age [12]. They are usually firm, bright red to purple, smooth papules ranging from 0.5 mm to 5 mm (Fig. 3). The frequency and number of cherry angiomas increase with age; an older individual may have anywhere from one to hundreds of lesions. Cherry angiomas most often present on the trunk and extremities and spare the mucosa. There may be a hormonal association given that they increase in frequency during pregnancy and involute post-partum.

Cherry angiomas are often asymptomatic but may bleed slightly with trauma. They do not require treatment but are often removed for cosmetic purposes or due to recurrent bleeding. They can be removed via snip excision, electrodesiccation, laser ablation, or with sclerotherapy [13, 14].

Dermatofibroma

Dermatofibromas are also referred to as cutaneous benign fibrous histiocytomas or sclerosing hemangiomas. They typically present in the second and third decade and are more common in women [15]. Their exact etiology is unknown, but there is

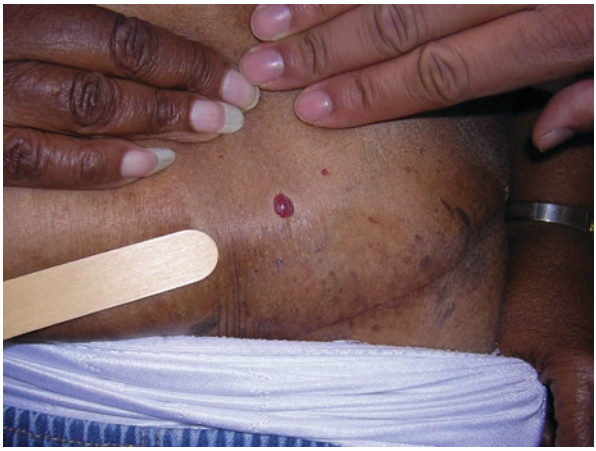

Fig. 3 Cherry angioma. (James Studdiford/Thomas Jefferson University)

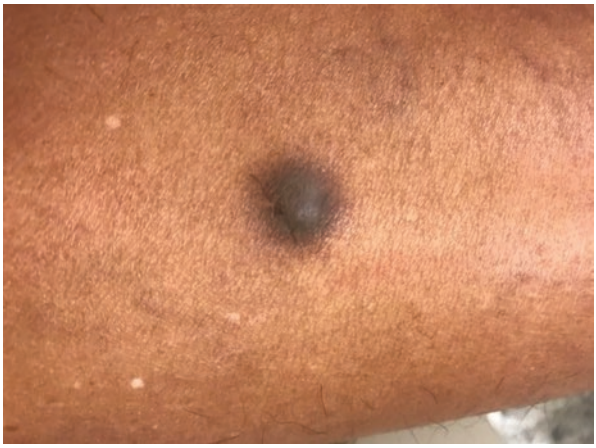

Fig. 4 Dermatofibroma. (Author)

evidence for both reactive and neoplastic processes [15, 16]. Synchronous development of multiple dermatofibromas has also been linked to autoimmune disease; most notable is systemic lupus erythematosus [16].

Dermatofibromas are firm, skin-toned to red-brown, minimally elevated, dome-shaped nodules usually measuring a few millimeters to 2 cm in diameter (Fig. 4). Rarely, they can form an area of depressed skin due to atrophy (atrophic dermatofibroma). They can occur on any cutaneous surface but do have a predilection for the lower extremities. Dermatofibromas are usually asymptomatic but can become pruritic or painful from trauma. They elicit a characteristic central depression (dimple sign) with lateral compression. On dermoscopy, a dermatofibroma classically appears as a peripheral pigment network with a central white patch [17].

Dermatofibromas do not require treatment but may be excised to exclude a melanocytic lesion or for cosmetic purposes. To reduce the risk of recurrence, dermatofibromas should be removed with a full-thickness excision, extending to the subcutaneous tissue. The resultant scar may be as noticeable as the original lesion.

Sebaceous Hyperplasia

Sebaceous hyperplasia is a common lesion that results from proliferation of sebaceous glands and is often misdiagnosed clinically as basal cell carcinoma. These lesions may be present at birth, with increasing incidence into the fourth through sixth decades. They are more common in males and have a high incidence in patients on long-term immunosuppression, especially those on cyclosporine or corticosteroids [18]. Sebaceous hyperplasia typically presents as small (1–4 mm up to 1 cm), soft, yellow-toned papules, often with central umbilication from which sebum can sometimes be expressed. They commonly appear on the face, with predilection for the forehead, nose, and cheeks but can also present on the chest and genitals (Fig. 5). They are diagnosed clinically; however, any concern for basal cell carcinoma would require biopsy. Lesions of sebaceous hyperplasia are benign and asymptomatic; however, patients often request removal for cosmetic purposes. Lesions can be treated with electrodesiccation or cryotherapy; phototherapy, laser therapy, chemical peels, isotretinoin, and surgical excision are alternative treatment options [19].

Milia

Milia (singular, milium) may occur in individuals of all ages and are seen in up to 50% of newborns [20]. They may arise congenitally, spontaneously (primary milia), or as a secondary process (secondary milia). Congenital and primary milia have a predilection for the face, often appearing on the cheeks, eyelids, and forehead, but can occur anywhere on the body. Secondary milia are associated with a wide array of diseases, medications, and trauma. Milia are small, 1–3 mm, white to yellow, superficial papules (Fig. 6). They are asymptomatic and diagnosed clinically. They tend to resolve spontaneously; however, secondary milia are more likely to persist.

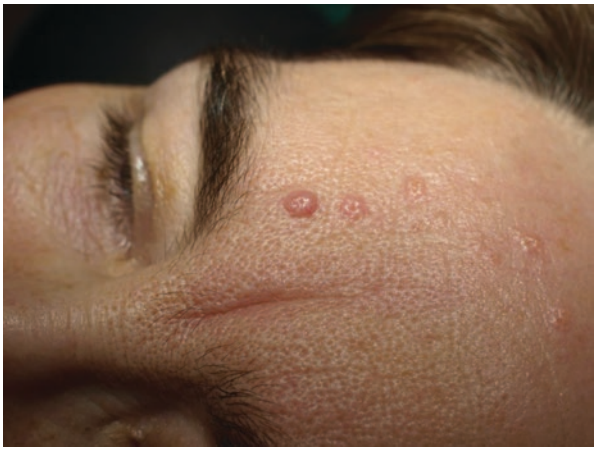

Fig. 5 Sebaceous hyperplasia**.** (WikiCommons—Klaus D Peter, MD)

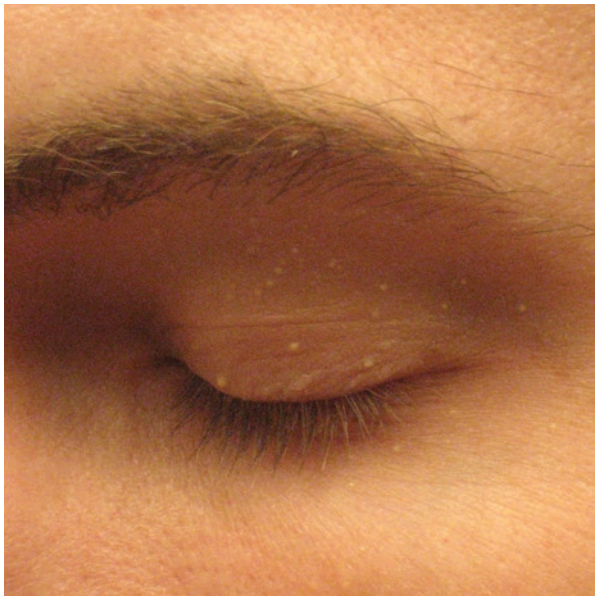

Fig. 6 Milia. (WikiCommons)

A single milium is typically treated by simple evacuation via incising/puncturing the papule with a needle or scalpel and expressing the contents with lateral pressure or with a comedone extractor. For multiple milia, topical retinoids, electrodesiccation, and laser ablation are effective [20].

Pyogenic Granuloma

Pyogenic granulomas are common vascular growths, also known as lobular capillary hemangiomas. Their name is a misnomer as they are not pyogenic nor granulomatous. They typically present in childhood through the second decade of life, with the mean age of onset being 6 years old [21]. There is a male predominance, but oral lesions are more common in females [22]. Their exact etiology is unknown, although they are thought to be due to a neovascularization process as they tend to occur after trauma [23]. Pyogenic granulomas appear most commonly on the head and neck, with a predilection for the cheek and oral cavity (especially in pregnancy). They may also be found on the trunk, upper extremity, and digits. They are usually a rapidly growing, pedunculated, erythematous papule, prone to bleeding and ulceration but otherwise asymptomatic (Fig. 7). They rarely regress spontaneously, and excision is often required to rule out amelanotic melanomas, which can have a very similar appearance. Treatment includes curettage with electrodesiccation, shave excision with electrocautery to the base, laser therapy, cryotherapy, and surgical excision [5, 21]. Due to pyogenic granulomas extending into the reticular epidermis, full-thickness excision is the most definitive treatment to avoid recurrence.

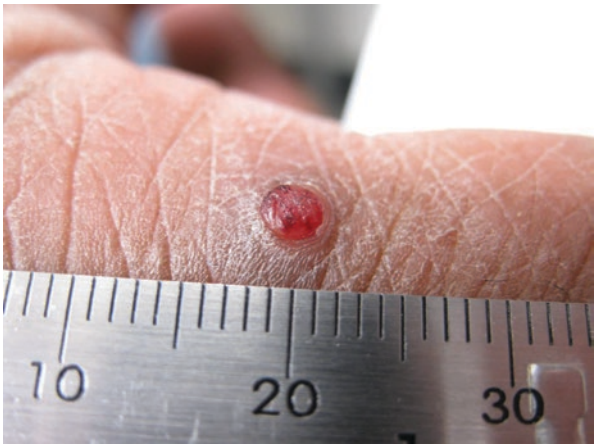

Fig. 7 Pyogenic granuloma. (By Kilbad at English Wikipedia, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=9568573)

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Skin Cancer for Primary Care

Joshua Trufant and Elizabeth Jones

Introduction

Skin cancer is the most commonly diagnosed cancer in the United States [1]. The US Surgeon General released a Call to Action to Prevent Skin Cancer in July of 2014, citing the elevated and growing burden of disease [2]. The vast majority of cutaneous neoplasms are basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), frequently referred to under the umbrella term "non-melanoma skin cancers." Approximately 5.4 million BCCs and SCCs are diagnosed each year (occurring in about 3.3 million Americans). BCCs make up roughly 80% of these tumors [3].

The incidence of non-melanoma skin cancer has continued to rise by 3–8% per year since 1960 in the United States. This pattern is seen in countries worldwide [4]. Death from these cancers is uncommon but occurs in roughly 2000 people each year in the United States [3].

Melanoma, while far less common, is associated with significantly higher mortality. In 2016, an estimated 76, 380 new cases of melanoma will be diagnosed, and 10,130 deaths from melanoma will occur [5]. The incidence of melanoma is expected to continue to increase in the United States [6].

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Common Skin Cancer Mimickers

Most skin lesions that cause concern for patients are benign. Nevi or "moles," seborrheic keratoses, solar lentigines, and cherry angiomas are exceedingly common, particularly as patients age. While these lesions can mimic cutaneous malignancies, in most cases they can be confidently diagnosed based on clinical grounds by their classic morphologic features. A primary care physician familiar with the various presentations of these benign neoplasms can spare a patient the anxiety of awaiting a specialist evaluation and also conserve healthcare dollars. When benignity is in doubt, biopsy or referral to a dermatologist is recommended. A few of the most common benign lesions bear mention.

Seborrheic keratoses (SKs) are typically pink to brown "stuck-on" appearing lesions frequently seen in middle-aged and elderly Caucasian populations (Fig. 1a). They may have a verrucous or mammillated surface (Fig. 1b), and their characteristic keratotic scale gives them a "waxy" appearance (Figs. 2 and 3). SKs arise on both sun-exposed and non-sun-exposed surfaces and, in some families, are inherited in an autosomal dominant manner. Patients frequently describe them as becoming irritated, crusted, or falling off on their own. Seborrheic keratoses are sometimes lightheartedly referred to by dermatologists as "barnacles" due to their widespread prevalence with increasing age. Darker lesions can appear almost black in color and are sometimes mistaken for melanoma.

Solar lentigines are tan to dark-brown macules (Fig. 4a) or small patches (Fig. 4b) that occur on sun-exposed areas. Historically referred to as "liver spots" or "age spots" by patients, these benign neoplasms increase in number with age (Fig. 4c). Unlike ephelides or "freckles" that arise early in life and fade with reduced sun exposure, solar lentigines increase in frequency and darkness with cumulative sun exposure and do not fade in winter months. Solar lentigines on the face can be particularly challenging to differentiate from the lentigo maligna subtype of melanoma in situ. Asymmetric growth or nonuniform darkening can raise suspicion for melanoma, but biopsy is frequently required to definitively rule out malignancy.

There are several common mimickers of basal cell carcinomas, including cherry angiomas, sebaceous hyperplasia, and fibrous papules. Bright red papules known as cherry angiomas frequently arise on the scalp, trunk, and extremities in patients (Fig. 5). These also increase in number with age and are typically asymptomatic. Rarely, they may become traumatized and turn purple or black and bleed, which might prompt patient or clinician concern for malignancy. Sebaceous hyperplasia typically presents on the central face as yellow papules with a central dell and telangiectatic vessels (Fig. 6). Their yellow hue and vessel pattern, which typically spares the center of the lesion, can help differentiate them from BCC. Fibrous papules, also known as angiofibromas, are benign skin-colored bumps often arising on the face, especially the nose (Fig. 7). They feel firm to the touch due to increased fibroplasia of collagen. Fibrous papules tend to have finer telangiectatic vessels than are commonly seen in BCC and rarely grow larger than 3–4 mm.

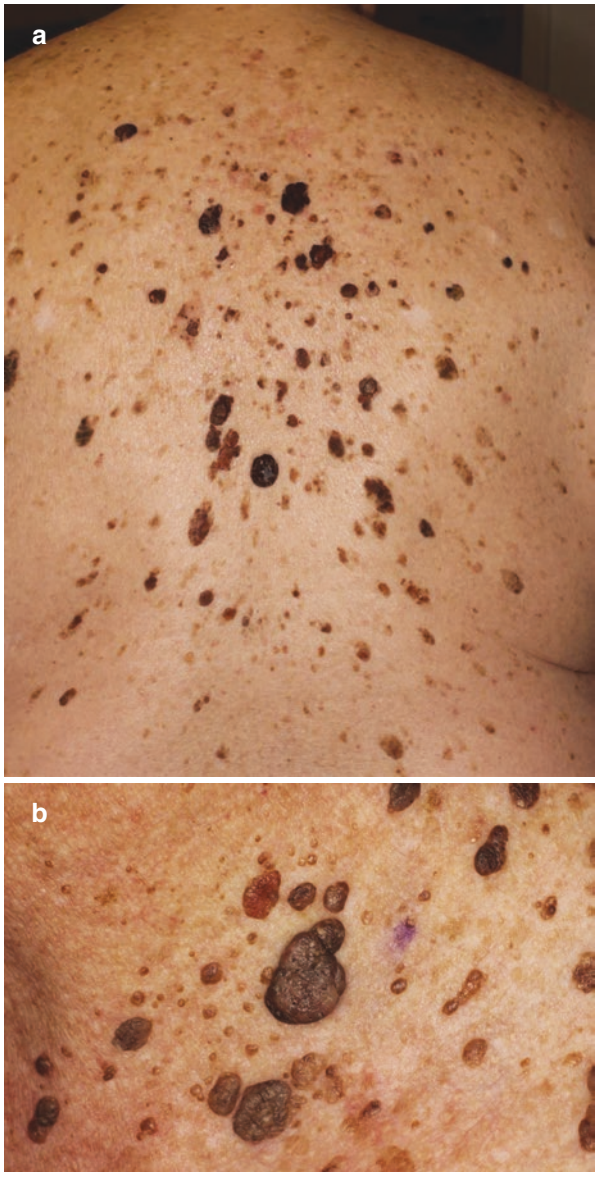

Fig. 1 (**a**) Multiple seborrheic keratosis on the back with a "stuck-on" appearance. (**b**) The surface is characteristically mammillated and waxy in appearance

Differentiating benign nevi or "moles" from malignant melanoma can be a challenge for primary care doctors and dermatologists alike, particularly when nevi are clinically atypical. Nevi can range in color from pink to tan to dark brown (Fig. 8a). Early lesions tend to be flat but gradually become raised with time, only to regress in elderly patients. Moles that present at birth are called congenital nevi. These nevi often have hair growth within them, a reassuring sign (Fig. 8b). The

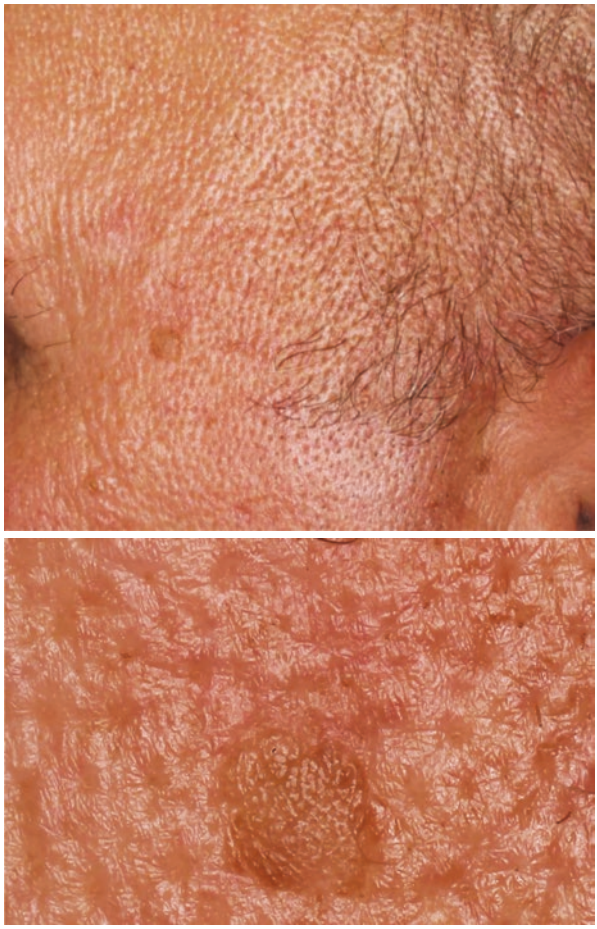

Fig. 2 Note the waxy appearance of this seborrheic keratosis

lifetime risk of melanoma developing in congenital melanocytic nevi is estimated to be up to 10% depending on the size [5]. Those with very large congenital nevi have a higher risk. Those with multiple irregular or large nevi are thought to also have an increased risk of skin cancer. Additional examples of nevi are shown in Fig. 8c–f.

Once the clinician is familiar with the morphology of common, benign lesions, it becomes easier to identify features that warrant higher diagnostic suspicion of malignancy. The "ABCDE" rule for identifying melanoma (A for asymmetry, B for border irregularity, C for color, D for diameter greater than 6 mm, and E for evolution) is an imperfect but easily remembered heuristic for patients and clinicians [7]. One major pitfall of this tool is its low specificity. The ABCDE rule is inclusive of changes frequently seen with other types of skin cancer, as well as numerous benign lesions. Furthermore, not all melanomas exhibit these features. When used by dermatologists, the sensitivity and specificity of a lesion with two of these criteria are

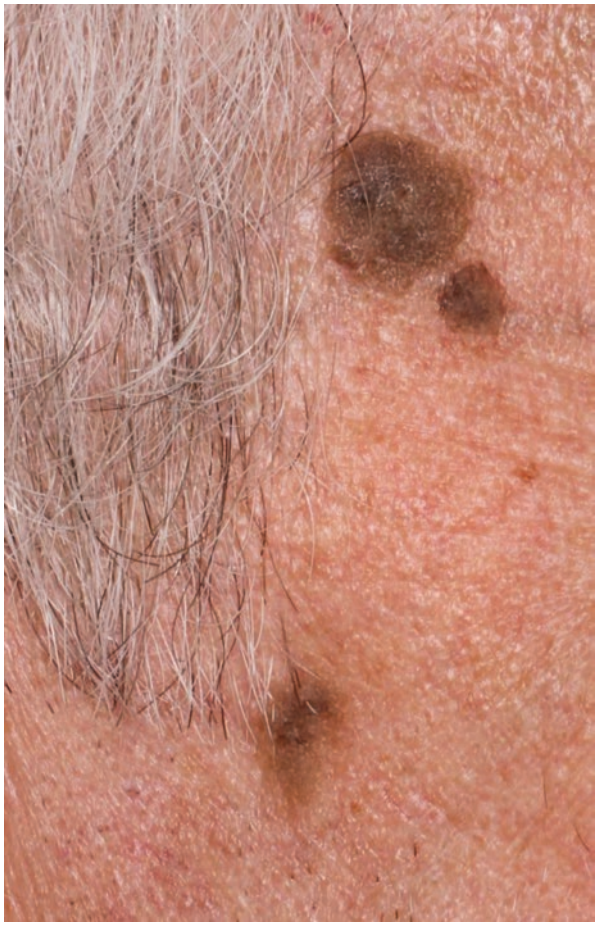

Fig. 3 Classic appearance of a seborrheic keratosis

89.3% and 65.5%, respectively [7]. Another proposed acronym is the "EFG" rule for melanoma, which stands for "evolving, firm, and growing," but this is not widely used or statistically validated.

Patient history can be helpful in identifying evolving lesions. An 8-millimeter diameter mole that has been present for years without change or symptomatic disturbance may be less worrisome than a new or changing 4 millimeter lesion. Recognizing a patient's most common nevus morphology, or "signature nevus" – perhaps oval and pinkish brown in a red-headed patient, for example – can reassure a clinician about a particular lesion's benignity when it fits this pattern or, contrarily, heighten suspicion for malignancy when it does not, the so-called ugly duckling sign (Fig. 9a–b) [7]. Other signs and symptoms such as rapid growth or color change, pain, tenderness, and ulceration are collectively concerning. New ulcerations that have grown or persisted beyond 1–2 months without resolution may warrant biopsy or close follow-up. A family history of

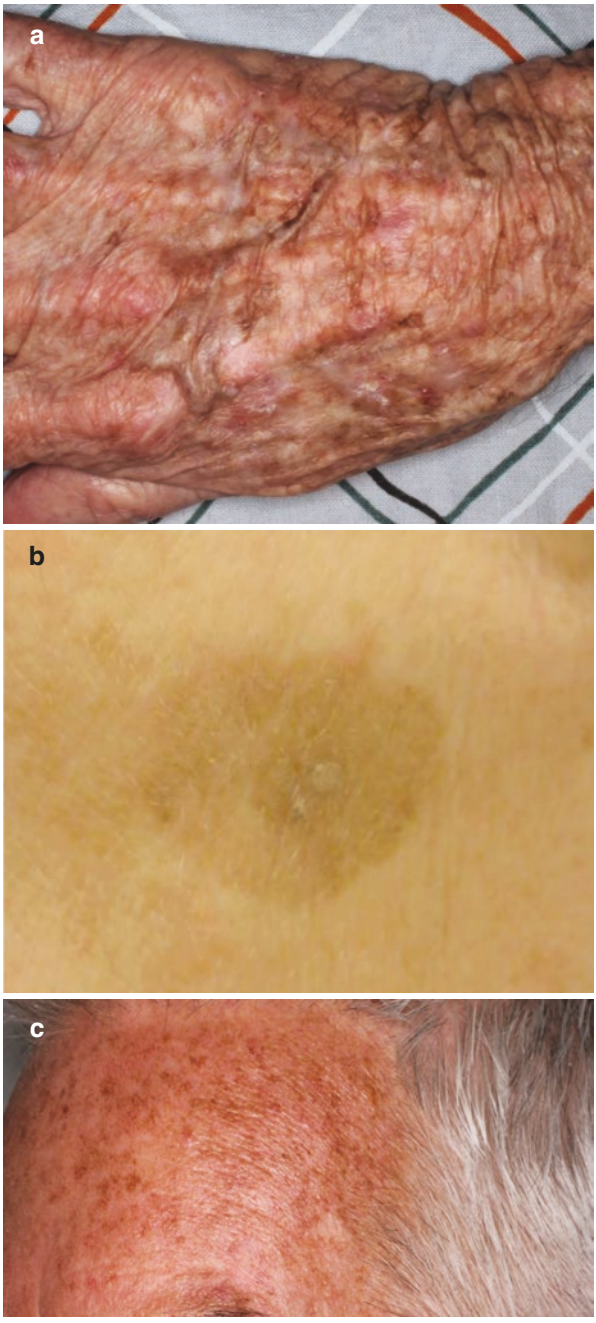

Fig. 4 (**a**) Solar lentigines. Note the light-brown photodistributed macules. (**b**) Larger solar lentigo with scalloped borders. (**c**) Light-brown similar-appearing lentigines

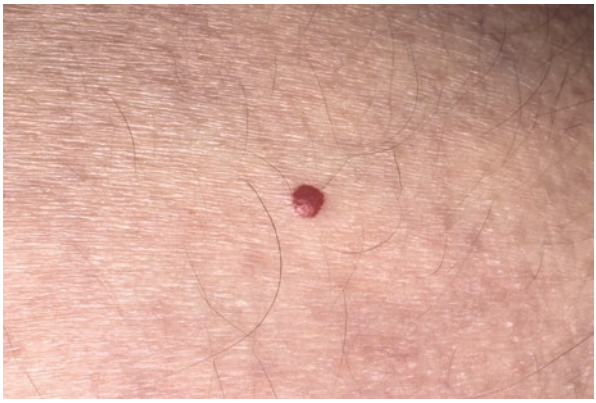

Fig. 5 Cherry angiomas – small, bright pink papule commonly located on the trunk

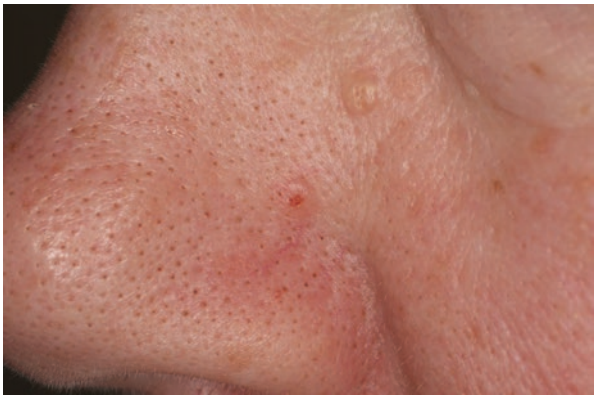

Fig. 6 Compare the superficial yellow papule with a central dell, a sebaceous gland hyperplasia (upper nasal sidewall) to a small BCC (lower nasal sidewall with central ulceration)

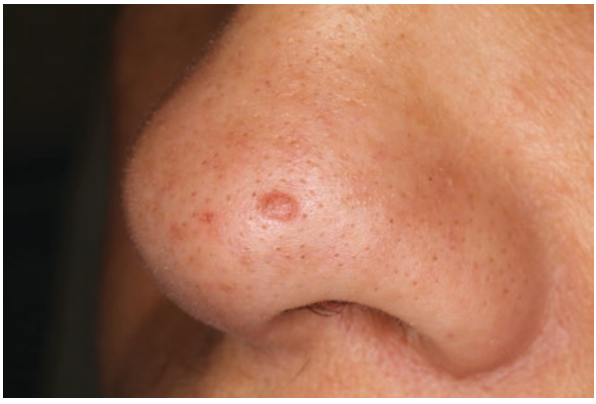

Fig. 7 Fibrous papule

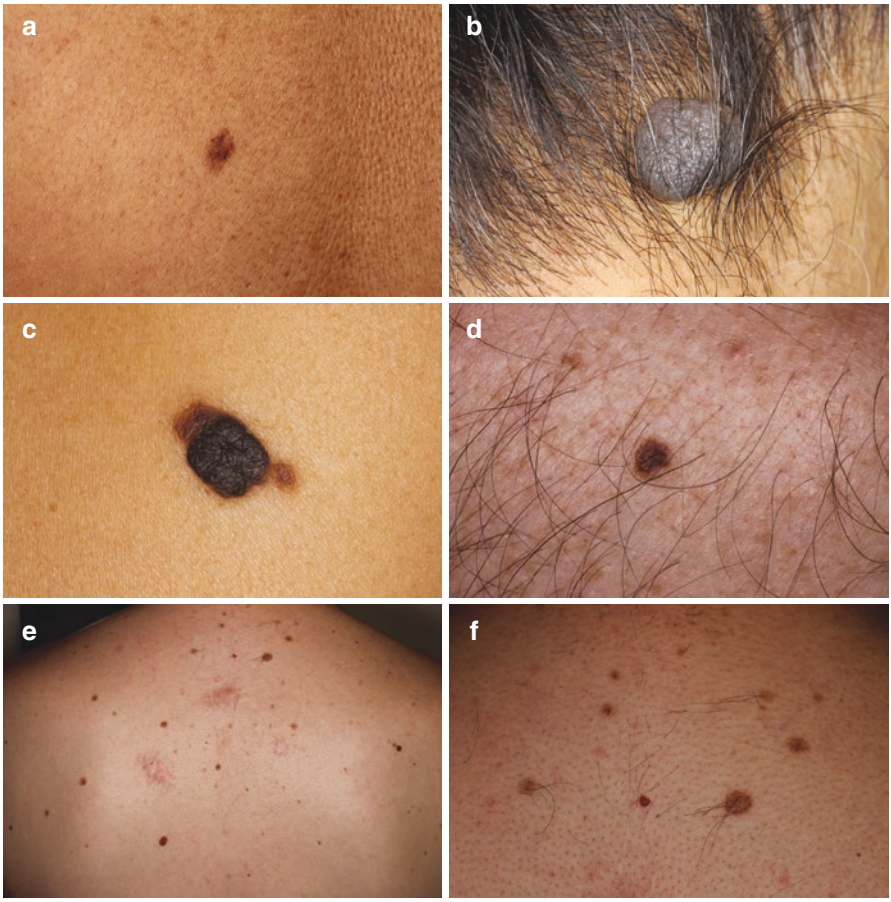

Fig. 8 (**a**) Benign mole. This mole has variation in color but overall has well-defined borders, felt soft, and, according to the patient, was present for years without change. (**b**) This mole, although larger, is soft, well-defined, and without ulceration or pain and has hair growth within, all reassuring signs. (**c**) This nevus, although not perfectly symmetric, is soft, painless, and fairly homogenously pigmented. (**d**) The classic appearance of a congenital pattern nevus. A small, round, well-defined evenly pigmented papule. (**e**) The back of a patient with multiple nevi. Note the scars from prior excisions of nevi which were benign in nature. (**f**) A close-up look at the congenital nevi of this patient. Note the symmetry, similarity in appearance, and homogenous pigmentation of these nevi

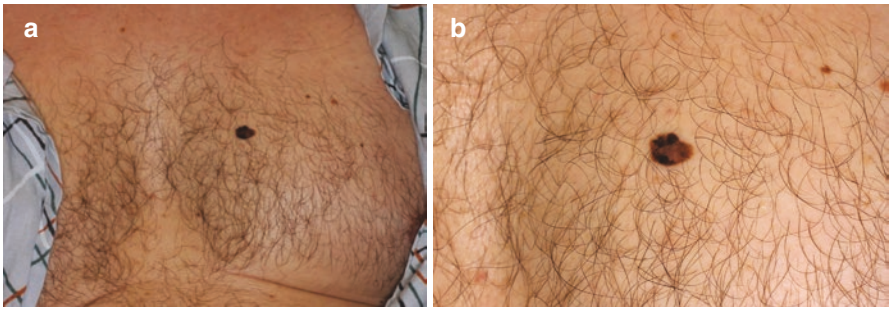

Fig. 9 (**a**) Melanoma in situ, context of the lesion. This lesion catches the eye of the examiner as it stands out from any other growth on the patient's chest, the "ugly duckling sign". (**b**) Melanoma in situ, up close. Note the irregular border, color variegation, asymmetry, and relatively large size of the tumor

melanoma or a high level of patient anxiety about a particular lesion may further lower a clinician's threshold for recommending biopsy.

Non-melanoma Skin Cancer

Non-melanoma skin cancer (NMSC) is associated with environmental, iatrogenic, and patient-related risk factors. Carcinogenesis due to UV radiation is believed to be mediated by direct DNA mutations via covalent bonding between adjacent pyrimidines and the formation of reactive oxygen species. Patients who are predisposed to photosensitivity, such as those with fair skin or red hair and blue eyes and those who always burn (categorized as Fitzpatrick skin type I), are at increased risk. The etiologic impact of human papillomavirus (HPV) has been demonstrated in genital and periungual SCC, as well as non-cutaneous head and neck SCC. Immunosuppressed patients, particularly organ transplant patients, are at high risk of developing SCC and require at least annual surveillance (Fig. 10). SCC risk is increased by 65-fold, or even higher, and BCC risk is increased by ten-fold in this population [8]. Tumors detected in these patients tend to be advanced and exhibit aggressive behavior [9]. A prior history of NMSC confers increased risk of additional skin cancers. Other

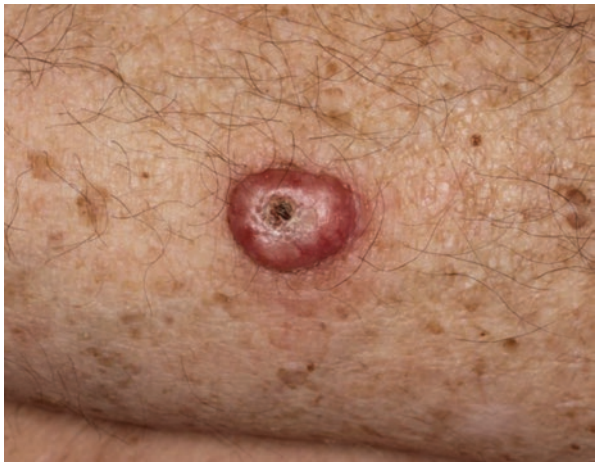

Fig. 10 Squamous cell carcinoma, keratoacanthoma subtype, diagnosed in a renal transplant patient on immunosuppression

risk factors include advanced age, radiation therapy, arsenic exposure, chronic inflammation, ulceration or scarring, and certain genetic mutations or syndromes.

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common cancer in humans. Its incidence worldwide is increasing by 10% per year. If this trend continues, the prevalence of this tumor will soon equal that of all other cancers combined [10]. BCC accounts for approximately 75–80% of non-melanoma skin cancer cases [3, 9]. While capable of local invasion and destruction, metastatic disease is exceedingly rare, occurring in less than 0.1% of all cases [9].

BCC, like SCC, is an epidermal tumor, but its true cellular origins and pathogenesis are less clear. Although previously thought to arise from the basal layer of the epidermis (hence its name), newer evidence suggests that BCC may originate from immature pluripotent cells of the interfollicular epidermis and outer root sheath of the hair follicle [11]. Cumulative sun exposure is an established risk factor for BCC, but the causal relationship with UV radiation is less clear for BCC than it is with SCC. The majority of BCCs have somatic mutations in the Hedgehog signaling pathway which regulates cell growth and differentiation during embryogenesis [11]. Inherited mutation of the *patched (PTCH)* gene, which encodes for a Hedgehog signaling pathway protein, is the cause of basal cell nevus syndrome, also known as Gorlin syndrome. The defect in syndromic cases is independent of external mutagenic stress, but the somatic *PTCH1* mutation is present in up to 68% of sporadic BCCs [10].

Basal cell carcinomas are divided into several major histologic subtypes: superficial, nodular, micronodular, or infiltrative, morpheaform, and pigmented. A single lesion commonly exhibits more than one histologic pattern. Superficial and nodular

BCCs, and their pigmented variants, are sometimes grouped together under the rubric of "low-risk" tumors. Deep invasion is rare (by definition in the superficial variant), and numerous treatment methods are curative. Nodular BCC is the most common subtype, comprising roughly 50–60% of cases. Nodular BCCs are commonly recognized as pink pearly papules, their "pearly" appearance (Fig. 11) attributed histologically to the mucinous stroma surrounding the aggregations of basaloid cells. These tumors tend to have well-defined, rolled, or indurated borders, with vascularity and translucency as key clues to their clinical diagnosis. Central ulceration may be present, historically referred to as a "rodent" ulcer because it appears to have been gnawed on by a rat (Fig. 12). Pigmented BCCs have irregular globules of pigment throughout the lesion (Fig. 13). A helpful diagnostic feature to the experienced eye, this feature may cause the neoplasm to mimic seborrheic keratosis, melanocytic nevi, or even melanoma.

Superficial BCCs comprise about one-fifth of diagnosed BCCs and occur on sun-exposed areas such as the head, neck, shoulder, and distal extremities [11]. They typically present as extremely thin pink to red telangiectatic papules or small

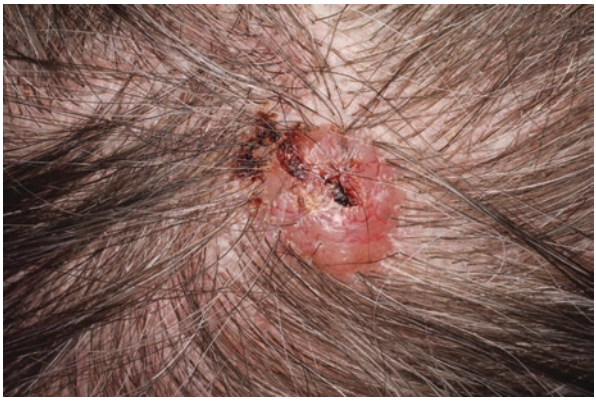

Fig. 11 Shown is the translucent, shiny quality of the surface of a BCC. Note the arborizing tortuous vasculature of this lesion

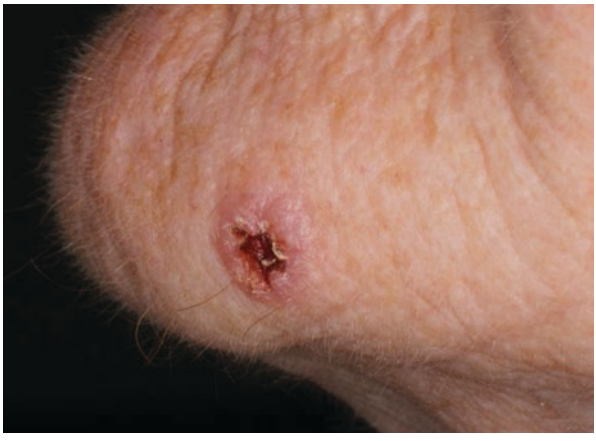

Fig. 12 Classic appearance of a rodent ulcer. Note the "pearly" shine with an almost translucent quality of the surface changes noted on this basal cell carcinoma

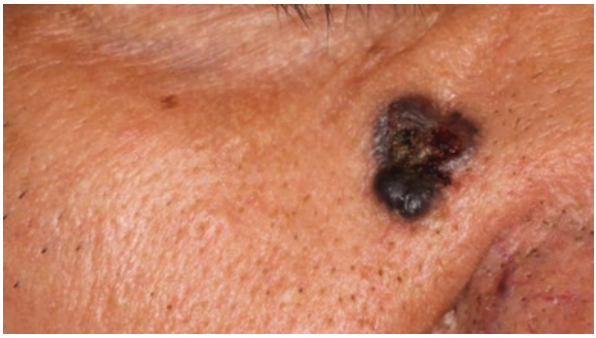

Fig. 13 Pigmented BCC with the characteristic shiny surface

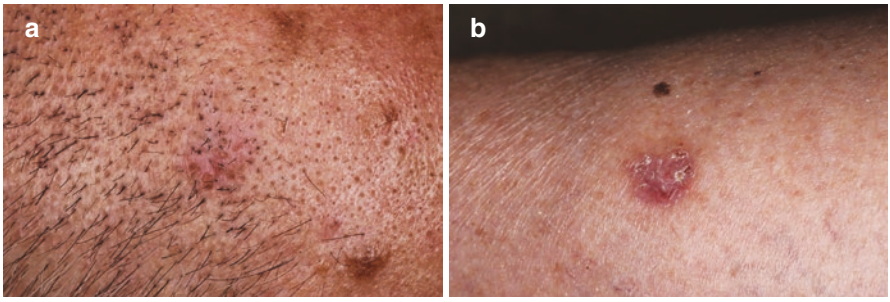

Fig. 14 (**a**) Superficial BCC, noted to appear as a thin pink plaque with keratotic scale. (**b**) Superficial BCC manifesting as a pink to red thin scaling plaque with keratotic scale and telangiectasias

plaques, sometimes with an overlying fine scale (Fig. 14a–b). They may exhibit a pearly or thin rolled border. Like nodular BCCs, they can also be pigmented with specks of blue, gray, brown, or black.

The higher-risk BCC subtypes – infiltrative, micronodular, and morpheaform – exhibit relatively aggressive behavior. Clinically, the micronodular and infiltrative subtypes present in similar fashion as nodular or superficial lesions but are characterized histologically by more deeply invading small islands or strands of basaloid cells. Morpheaform BCCs typically present as slightly depressed, firm, ill-defined pink or skin-colored sclerotic plaques, resembling scars. The morpheaform and infiltrative subtypes tend to have a higher recurrence rate as compared to other subtypes of BCC [12]. They sometimes show perineural invasion, a poor prognostic feature. Another subtype of BCC, the fibroepithelioma of Pinkus, is a skin-colored to pink sessile nodule that favors the trunk, particularly the lower back, and may resemble a skin tag.

Most basal cell carcinomas occur on the head and neck, with the nose being the most common location. Periorbital areas should not be neglected on examination, as BCCs here may be missed without close inspection of the medial canthus (Fig. 15a) and upper and lower lid margins (Fig. 15b). Patients who wear glasses should be asked to remove them prior to examination. Large, arborizing vessels traversing the

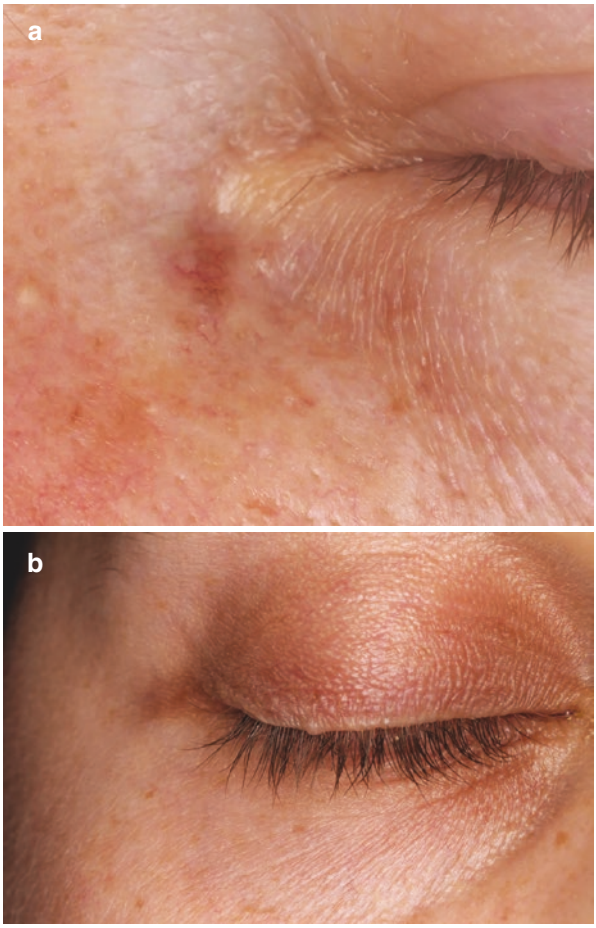

Fig. 15 (**a**) Periocular BCC. Note arborizing telangiectasias on the medial canthus. This required two stages of Mohs micrographic surgery to excise completely. (**b**) Note the small papule which is a subtle BCC on the upper eyelid. The key feature here is the translucent nature of its clinical appearance

lesion is a common clue of malignancy and can help the clinician differentiate BCC from sebaceous hyperplasia or fibrous papules, which are also very common on the face as mentioned earlier. Patient history can be useful to distinguish BCCs from inflammatory or vascular lesions, which may also be pinkish red and papular. A "pimple" or sore that does not heal after 1–2 months warrants closer examination or biopsy to rule out skin cancer.

Actinic Keratoses

Actinic keratoses (AKs), sometimes called solar keratoses or "pre-cancers," are potential precursors of squamous cell carcinoma (SCC). They occur on sun-damaged areas, mainly on the head and neck, upper trunk, and distal extremities, and are typically accompanied by other signs of photoaging, such as lentigines,

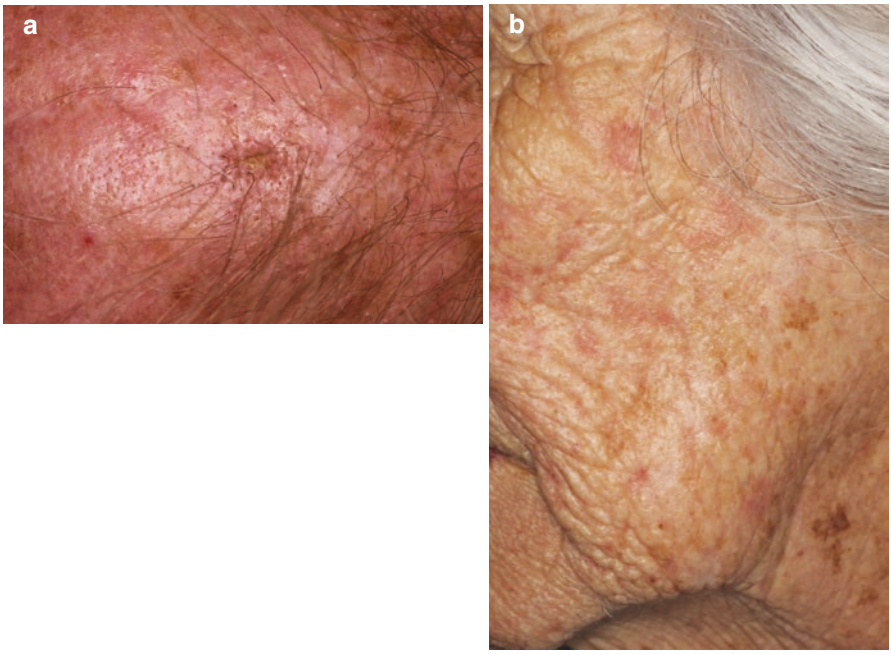

Fig. 16 (**a**) Note the brown keratotic crust overlying erythema. The rough "sandpaper-like" feel of this lesion is characteristic of an actinic keratosis. (**b**) Note multiple pink scaly actinic keratoses on the lateral cheek of this patient

rhytides (wrinkles), mottled pigmentation, and telangiectasias. They are rough or gritty on palpation, sometimes more easily felt than seen. They tend to feature keratotic scale and can range in color from pink to brown (Fig. 16a–b). Erythema may be subtle or absent, and overlying scale can become heaped up or form what is known as a "cutaneous horn." Variants include hyperplastic (typically thicker), pigmented (light to dark brown), lichenoid (pink, inflamed), and atrophic AKs, as well as actinic cheilitis of the vermillion lip. Estimates of an individual lesion's propensity to evolve into SCC vary widely in the literature. One study found that the average number of AKs in affected patients is 7.7, with an accompanying 10% risk of developing SCC over 10 years [13].

Squamous Cell Carcinoma

Studies have demonstrated that SCC arises sequentially after an accumulation of genetic damage. Over 72% of SCCs develop from AKs or areas of actinically damaged skin, referred to as underlying "field cancerization" [14]. The most common mutations found in SCC affect the p53 tumor suppressor gene; others include *WNT*, *Ras*, *p16INK4*, *NF-kB*, and *c-Myc* [9, 15]. Tenderness may be a sign of

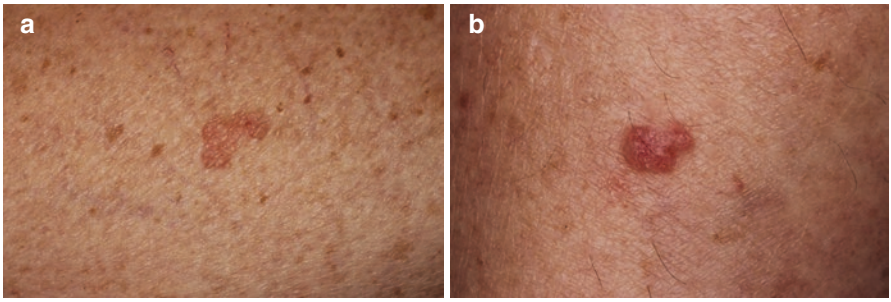

Fig. 17 (**a**) This squamous cell carcinoma in situ resembles a pink small plaque of psoriasis or eczema. (**b**) Bowen's disease showing a single pink plaque with keratotic scale

progression from AK to SCC, although pain or paresthesias are frequently absent in cutaneous malignancies. Squamous cell carcinoma in situ or Bowen's disease, the most superficial form of SCC, may present similarly to AK but tends to have a thicker and more erythematous papular or plaque component underlying the gritty scale. It may resemble a single plaque of psoriasis or eczema (Fig. 17a–b). Invasive SCC lesions may be exophytic or verrucous and can ulcerate (Fig. 18a) or form a firm keratotic scale-crust (Fig. 18b). Like AK, a cutaneous horn may develop from SCC (Fig. 19a) although horns can arise from warts (Fig. 19b), seborrheic keratoses, and other benign growths as well. Lesions are described on both sun-exposed and non-sun-exposed skin. Human papilloma virus has been implicated in the development of genital and periungual SCC. A "wart" in either region that has not resolved with conservative treatment should raise suspicion for malignancy.

Keratoacanthoma is a subtype of SCC characterized by a rapid, eruptive growth pattern. The typical presentation is a dome-shaped papule or nodule with a central crateriform invagination or dell that may grow to become several centimeters in diameter over a period of weeks (Fig. 20a–b). A subset of lesions will then regress spontaneously, which has led to debate over the true malignant potential of KAs. However, due to their rapid growth and ability to invade and distort the skin, they usually are treated in the same manner as other types of SCC.

SCC is associated with a low but significant rate of metastasis, of approximately 3–5% [16]. A small subset of tumors is believed to be responsible for most of the SCC-associated morbidity and mortality. Various clinical criteria have been proposed for identifying this "high-risk" group, including diameter greater than 2 cm, location on the ear, lip, temple, or anogenital region, rapid growth, recurrence after treatment, patient immunosuppression, associated neurologic symptoms, and tumors arising in areas of prior radiation therapy or chronic inflammation. High-risk histologic features include poor cellular differentiation, perineural, lymphatic, or vascular invasion, and invasion beyond the subcutaneous fat [17, 18]. Tumors that meet "high-risk" criteria have metastasis rates up to 30% [19].

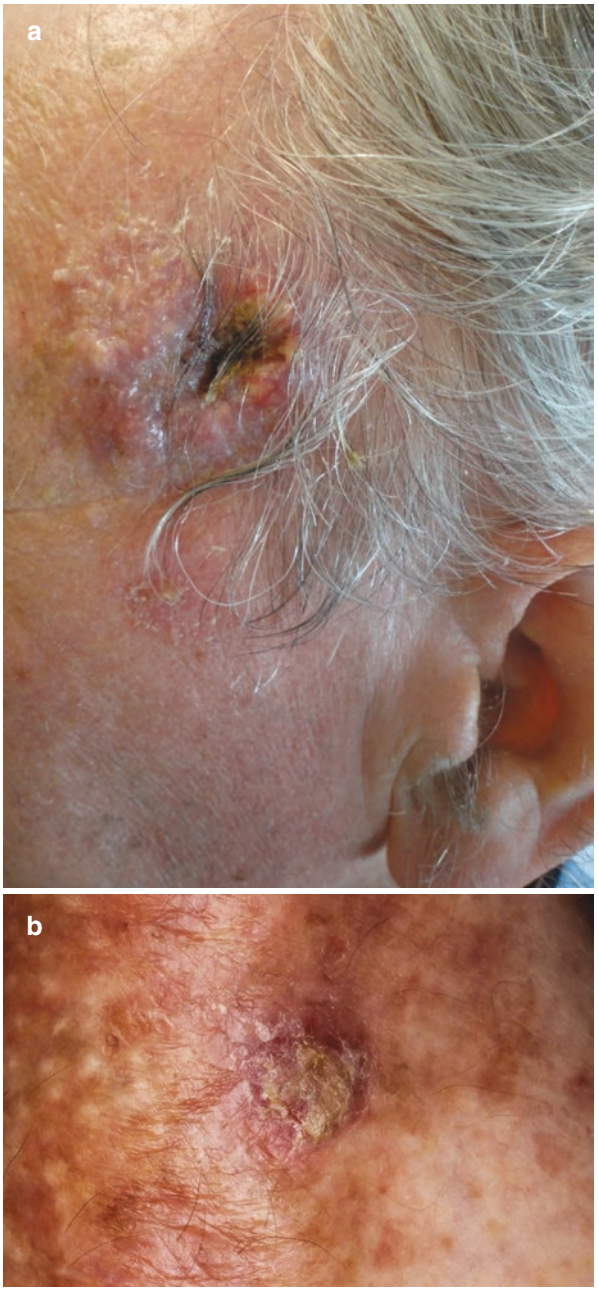

Fig. 18 (**a**) Note large ulceration of this squamous cell carcinoma. (**b**) A squamous cell carcinoma with keratotic crust and erythema at its base on the background of sun-damaged skin

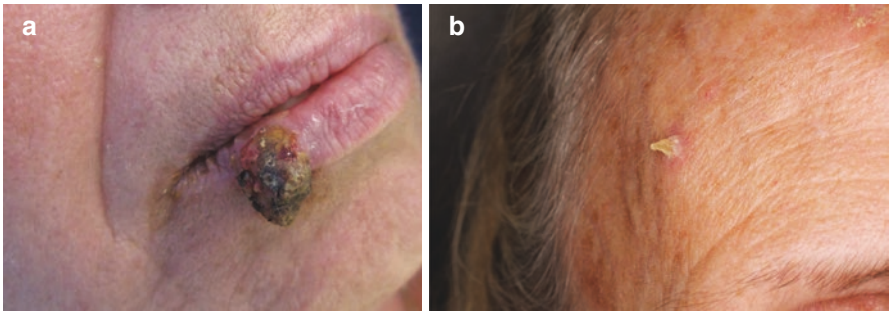

Fig. 19 (**a**) See the cutaneous horn-like verrucous appearance of this SCC. (**b**) A classic appearance of a cutaneous horn. The final diagnosis of this lesion was confirmed to be a wart, although a biopsy was performed in this case to rule out squamous cell carcinoma

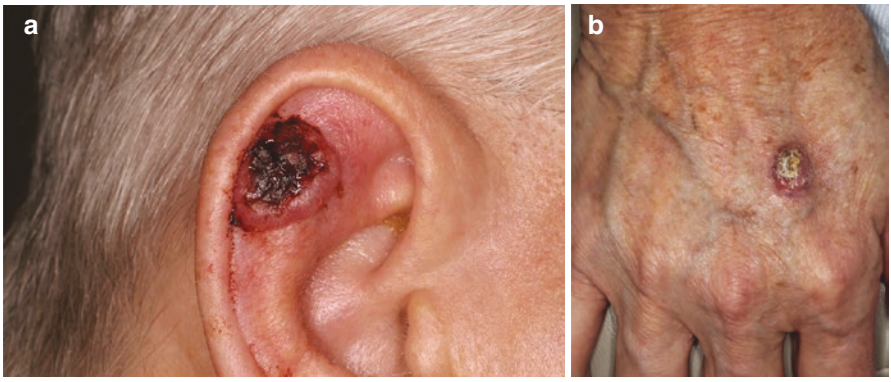

Fig. 20 Keratoacanthoma. Classic dome-shaped nodules with central crateriform ulceration in the center. The ulceration may show either hemorrhagic (**a**) or keratotic (**b**) crust or both

Diagnosis and Treatment of NMSCs

The US Preventive Services Task Force (USPSTF) has concluded that there is insufficient evidence to assess the risks and benefits of visual skin examination by clinicians [1, 20]. The Task Force's inability to recommend visual screenings reflects the paucity of methodologically rigorous studies of the impact of clinician screening on skin cancer morbidity and mortality. Dermatologists most frequently perform full-body visual skin exams. PCPs play a large and important role in detecting cutaneous malignancies during intentional skin-focused exams, as well as during incidental

detection when evaluating other organ systems. A survey of US physicians in 2005 reported that 81% of dermatologists, 60% of primary care physicians, and 56% of internists reported performing a full-body skin cancer screening examination on their adult patients [21]. Studies of non-melanoma skin cancer detection are lacking, but PCPs have been shown to be moderately accurate in diagnosing melanoma, with a sensitivity of 42–100% and a specificity of 70–98% [1]. Most of this data is based on clinician examination of skin lesion images rather than live patient assessment. A meta-analysis of 32 studies was performed to compare the accuracy of dermatologists and primary care physicians in identifying melanoma. For diagnostic accuracy, dermatologists showed a sensitivity of 0.81–1.00, as compared to 0.42–1.00 for PCPs [22]. This study was unable to show differences in diagnostic, biopsy, or referral accuracy between dermatologists and PCPs. Detection of skin cancers at earlier stages allows for improved outcomes; further research is needed on the role of the clinician's full-body skin examination on skin cancer prevention, detection, and outcome.

Biopsy Techniques

Highly suspicious skin lesions should be biopsied or referred to a specialist for further evaluation to rule out malignancy. Shave biopsy is the most common method used by dermatologists to acquire a specimen for histopathologic analysis. After injection of local anesthesia – usually 1% lidocaine with epinephrine for added hemostasis – the clinician uses a scalpel or straight-edged blade to remove all or a portion of an exophytic lesion's surface, leaving a wound that is flush with the surrounding epidermis. A "scoop" shave can be performed to obtain greater depth, but the clinician typically does not attempt to penetrate beneath the dermis. Hemostasis is achieved with application of aluminum chloride solution, electrodesiccation, and/or a pressure dressing. If a deeper specimen is desired, a punch biopsy may be used to include subcutaneous fat as well. The cylindrical cutting edge of a punch biopsy tool resembles a tiny (2–8 mm) "cookie-cutter," which is twisted while applying downward pressure to reach the subcutaneous fat. The freed tissue is then removed with forceps, and the small cylindrical wound heals by secondary intent or by closure with a suture. If suspicion is high for melanoma, where accurate depth assessment is essential to guide treatment and prognosis, and prompt treatment may theoretically reduce mortality, an excisional biopsy of the entire clinically apparent lesion or an incisional biopsy of a portion of a lesion can be obtained with a scalpel or punch biopsy and closed with sutures. If the clinician identifies classic features of a non-melanoma skin cancer, a curette used to scrape, sample, or debulk a tumor can be both diagnostic and therapeutic, particularly when combined with electrodesiccation. The curette method does not allow for histological confirmation of cure and is never recommended if melanoma is a consideration.

Surgical Treatment

Destructive Modalities

A number of techniques are effective in treating low-risk forms of NMSC. Electrodesiccation and curettage (ED&C) is a long-employed method that can be applied to smaller, well-defined, and/or superficial NMSCs in less cosmetically sensitive or functionally important areas [19]. A systematic review of primary BCC treated by ED&C over a 40-year period showed a 5-year recurrence rate of 7.7%, comparable to all other physical modalities excepting Mohs micrographic surgery (MMS) [23]. Recurrence rates are higher for more invasive forms of BCC and high-risk SCC, making this an unsuitable option for treatment of these lesions. Healing time following ED&C is typically longer than that of sutured wounds. Scarring may be less optimal, particularly in hair-bearing areas. Despite its shortcomings, ED&C is a less expensive, less invasive, and less time-consuming alternative to traditional surgical excision with similar cure rates in low-risk NMSC. Careful patient and tumor selection is important in choosing this route of treatment, as there is no histologic confirmation of cure.

Cryosurgery utilizes liquid nitrogen to destroy tumor cells through freezing. Most commonly used to treat pre-cancerous actinic keratoses, cryosurgery is also applied to low-risk NMSC subtypes, particularly in the elderly or poor surgical candidates. The systematic review of primary BCC treatment mentioned above showed a 7.5% 5-year recurrence rate following cryosurgery [21]. Like ED&C, cryosurgery is not recommended for invasive or high-risk NMSC in younger patients due to significantly higher recurrence rates. Another drawback is the high degree of operator-dependent variability in outcomes, which reflects differences in tumor selection, duration of treatment, and number of freeze-thaw cycles. Pain, erythema, and blistering are potential transient side effects, but hypopigmentation, a result of melanocytes' increased sensitivity to freezing, can be permanent. Hypopigmentation is almost guaranteed in dark-skinned individuals.

Wide Local Excision

Traditional wide local excision (WLE) of non-melanoma skin cancers typically includes a 3–5 mm margin of normal skin around the clinically visible tumor. If the clinician intends to suture the surgical wound, triangular-shaped "dog ears" must be excised on either side to create a linear scar that will contour to the surrounding skin. Alternatively, the clinician can design a fusiform or "football-shaped" excision initially, with the skin cancer and margin of normal skin at the center and tapered ends on either side (Fig. 21). The surgical specimen is typically excised at the level of the mid-subcutaneous fat. It's then placed in formalin, embedded in paraffin, and cut into vertical sections for margin examination by a pathologist. Standard excision

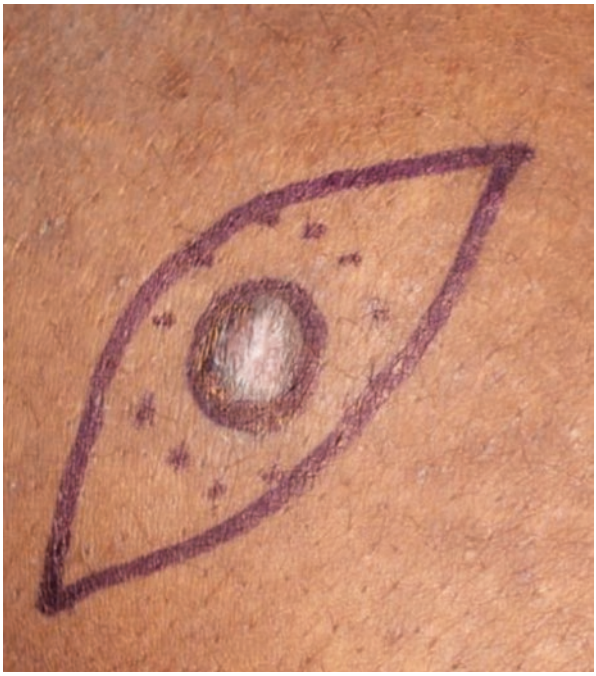

Fig. 21 Fusiform design of an excision

with a predetermined margin of normal skin as outlined above has shown to provide 5-year cure rates of approximately 98% for BCC and 92% for SCC [24–26].

While the NCCN guidelines for BCC advocate for 4 millimeter margins with postoperative margin evaluation, the margin taken ultimately depends on the definition of a tumor's borders, its anatomical location, and histologic subtype, among other factors. For low-risk squamous cell carcinoma, NCCN guidelines advocate 4–6 millimeter margins with postoperative margin evaluations [17]. Wider excisions and Mohs micrographic surgery are recommended for high-risk SCC.

Mohs Micrographic Surgery

Mohs micrographic surgery (MMS) is a tissue-sparing technique that achieves the highest cure rates for non-melanoma skin cancer. Developed in the 1940s by Frederic Mohs, a general surgeon at the University of Wisconsin, the technique has evolved to employ real-time frozen sectioning and histopathologic analysis of excised tissue. MMS has a 5-year cure rate of 99% for untreated BCC and 97% for SCC [23, 24]. For locally recurrent tumors, repeat treatment by surgical excision has been reported to have a local recurrence rate of 23.3% as compared to 10% by MMS for SCC [24]. For high-risk SCC, the 5-year cure rate for traditional surgical excision is 77%, as compared to 90–94% for MMS [27]. Higher MMS cure rates are due not only to intraoperative margin assessment but also to the unique method by

which tissue specimens are processed, which allows for assessment of 100% of the peripheral and deep tissue margins, as compared to less than 1% of the margin examined by traditional vertical sectioning [19]. Should the tumor extend to the margin of tissue excised after the first "stage" or "layer," the Mohs surgeon then excises additional tissue only in the area of margin positivity. Frozen sectioning and histopathologic analysis is then performed on the new specimen. This process is repeated until clear margins are achieved.

Complete, real-time margin assessment allows the Mohs surgeon to excise tumors with narrower margins than traditional WLE, thereby sparing more healthy tissue. This is extremely important in cosmetically sensitive areas such as the face and in areas of limited tissue volume and laxity such as the hands, feet, and genitalia. It also allows the Mohs surgeon to confidently reconstruct wounds with local skin flaps or grafts, which significantly rearrange tissue and would complicate re-excision after failed WLE. Application of MMS to a wider variety of cutaneous malignancies, including dermatofibrosarcoma protuberans (DFSP), Merkel cell carcinoma, and melanoma, has shown promising results, in many cases exceeding cure rates associated with WLE.

Nonsurgical Treatment Modalities

Topical Treatments

Some early, superficial forms of NMSC may be treated by patients at home with serial application of topical creams. Imiquimod is a topical immunomodulator that binds to the T-cell surface toll-like receptor 7, thereby stimulating a robust local immune response that destroys the tumor cells. It is FDA-approved for the treatment of warts, actinic keratoses, and superficial BCC in immunocompetent patients. The 5-year clinical clearance rate with imiquimod monotherapy for biopsy-confirmed superficial BCCs is about 80% [11]. 5-Fluorouracil (5-FU), a pyrimidine analog antimetabolite that directly targets rapidly dividing tumor cells, has been a mainstay of systemic chemotherapy regimens for many years. Its topical formulation, available in several concentrations, is also FDA-approved for the treatment of actinic keratoses and superficial BCC. One study of nonsurgical treatment modalities found tumor-free survival at 3 years posttreatment was 68.2% for fluorouracil versus 79.7% for imiquimod [28]. A third agent, ingenol mebutate, was approved in 2012 for treatment of actinic keratosis only. It has the advantage of a shorter, 3-day course, as compared to 4–6 weeks of daily application of 5-FU or imiquimod. While none of the topical agents are FDA-approved for SCC, in practice they are often used to treat in situ disease. The most common side effect is application site inflammation and irritation, which can be so severe as to be treatment-limiting. Another drawback of topical therapies, as with all nonsurgical modalities, is the lack of histologic confirmation of cure, a particular concern when a superficial biopsy may underestimate the true depth of tumor invasion.

Photodynamic therapy (PDT) involves application of a topical photosensitizer precursor, either 5-aminolevulinic acid (5-ALA) or methyl aminolevulinic acid (MAL), prior to exposure to a visible light source. Tumor cells preferentially convert the topical agent to protoporphyrin IX, a photoactive compound that leads to cytotoxic free radical formation when stimulated by blue or red light. Natural light or "daytime" PDT, which obviates the need for an artificial light source, is gaining in popularity, though its effectiveness is not yet proven. 5-ALA, the only agent available in the United States, is FDA-approved for treatment of actinic keratosis but, like the other topical agents, is often used to treat superficial NMSC. It is particularly useful in patients with larger areas of field cancerization. Most studies of PDT efficacy are limited by short follow-up periods, but few with 5-year follow-up data show superficial or in situ NMSC cure rates similar to destructive modalities like cryotherapy [29]. Thicker tumors are more resistant to treatment due to the limitations of topical agent and visible light penetration. PDT is not recommended for high-risk BCC or SCC.

Radiation

Radiation therapy is a moderately effective NMSC treatment option for patients who are deemed poor surgical candidates due to advanced age or medical comorbidities. It may also function as an adjunctive therapy or for palliative care for symptomatic relief of incurable cancers. A meta-analysis of radiotherapy treatment of BCC found an overall 5-year cure rate of 91.3%. A similar study showed a 5-year cure rate of approximately 90% for SCC [23, 24]. However, cure rates are lower for larger lesions. Areas of the head and neck tolerate radiation better than skin on the trunk and extremities [30]. Early side effects of radiation include headache, nausea, vomiting, skin irritation, hair loss, and fatigue. Late reactions can occur years after treatment and include telangiectasias, epidermal atrophy, and altered pigmentation. Late soft tissue and cartilage necrosis is rare, and the risk is reduced with smaller doses [31].

Systemic Treatment

Systemic therapy is typically reserved for locally advanced, unresectable, or metastatic NMSC. Vismodegib is an oral medication that targets a protein involved in the Hedgehog signaling pathway, commonly mutated in BCC. A two-cohort nonrandomized study revealed a 30% response rate in metastatic BCC and a 43% response rate in patients with locally advanced BCC [32]. Vismodegib is also sometimes used to treat basal cell nevus syndrome, in which patients can develop hundreds of BCCs. Unfortunately, in addition to its limited efficacy, the drug is often poorly tolerated. Side effects include painful muscle spasms, loss of taste, gastrointestinal discomfort, fatigue, alopecia, and hyponatremia [33]. Newer, related formulations are plagued by similar problems. Still, for a small group of unfortunate patients, this family of medicines represents a tumor-specific treatment option where none existed before.

Treatment of locally advanced or inoperable SCC typically involves radiation therapy with or without chemotherapy. Cisplatin with or without 5-fluorouracil, although rarely curative, is the mainstay of systemic treatment of metastatic SCC. More recently, cetuximab, a monoclonal antibody that inhibits the epidermal growth factor receptor, has shown some promise as mono- or adjuvant therapy with radiation or surgery for treatment of locally advanced SCC [34]. Immune checkpoint inhibitors are also being studied as a future treatment option.

Follow-Up of NMSCs

According to NCCN guidelines, lifetime biannual to annual follow-up visits with a clinician are recommended after diagnosis and treatment of a NMSC. These visits serve as opportunities both to evaluate for recurrence and screen for new cutaneous malignancies. High-risk patients, in particular organ transplant recipients, may require more frequent screening, while the extremely elderly may warrant less frequent visits. One meta-analysis reported that the risk of developing a second NMSC within 3 years of the first is 18% for SCC and 44% of BCC [35]. A separate prospective study reported that after a diagnosis of a single BCC or SCC, the 5-year risk of developing an additional non-melanoma skin cancer was 50% overall, 41% for BCC, and 31% for SCC [36]. The risk of future NMSC increases with the diagnosis of additional NMSC. For many patients then, a new NMSC is not a question of "if" but "when." The vast body of literature suggests that earlier detection and treatment leads to higher cure rates and less tumor- and treatment-related morbidity.

Melanoma

The incidence of cutaneous melanoma has risen rapidly over the past 30 years, and rates continue to climb, particularly in patients 50 and older [5]. The annual incidence rate is 25/100,000 in non-Hispanic whites, 4/100,000 in Hispanics, and 1/100,000 in blacks. Below age 50, incidence rates are higher in women, but rates in men double and triple as compared to women by age 65 and 80, respectively. The lifetime risk for a diagnosis of melanoma is 1.94% for males and 1.30% for females [1].

Melanoma accounts for only 1–5% of skin cancer diagnoses but is associated with at least 75% of skin cancer deaths [1]. Although incidence has steadily increased, overall mortality rates are stable since the 1980s. This is likely due to a disproportionate increase in early diagnosis of in situ or superficial tumors, when surgical cure rates are highest. The 5- and 10-year survival rate is 98% for localized melanoma (84% of cases) and declines to 63% and 17% for regional and distant metastatic disease, respectively [2]. Tumor thickness, known as Breslow depth, and sentinel lymph node status are the most important prognostic factors.

Patient risk factors for melanoma include age, male sex (in patients over 50 years of age), skin type (red or blonde hair, lightly colored skin with multiple freckles, blue or hazel eyes), sun sensitivity, multiple dysplastic nevi (5 or more), a total nevi count greater than 100 or the presence of atypical nevi, and a personal or family history of melanoma and a history of NMSC [20]. The number of known genetic mutations that confer increased risk of melanoma is steadily climbing. One of the most well-described mutations occurs in the tumor suppressor gene *CDKN2A*. An autosomal dominant mutation in *CDKN2A* causes familial atypical multiple mole melanoma syndrome (FAMMM), which is associated with multiple clinically atypical nevi (often totaling more than 50) and an increased risk of melanoma [37]. Studies have shown that an increased number of dysplastic nevi is associated with a 6.4-fold increase in the risk of melanoma [20]. Environmental factors such as ultraviolet radiation exposure, sunburns, and artificial tanning bed use are thought to increase the risk of melanoma [20, 38]. However, it is important to note that melanoma can occur in any race on both sun-exposed and non-sun-exposed surfaces.

The World Health Organization (WHO) recognizes four major melanoma subtypes: superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), nodular melanoma (NM), and acral lentiginous melanoma (ALM). In practice, however, many melanomas do not fit neatly into a single category.

Superficial spreading melanoma (SSM), the most common subtype, is characterized by an initial, radial growth pattern. It classically presents as a pigmented macule or thin papule or plaque, most commonly on the trunk in men and the legs in women. SSM may have jagged, irregular borders and color variegation from

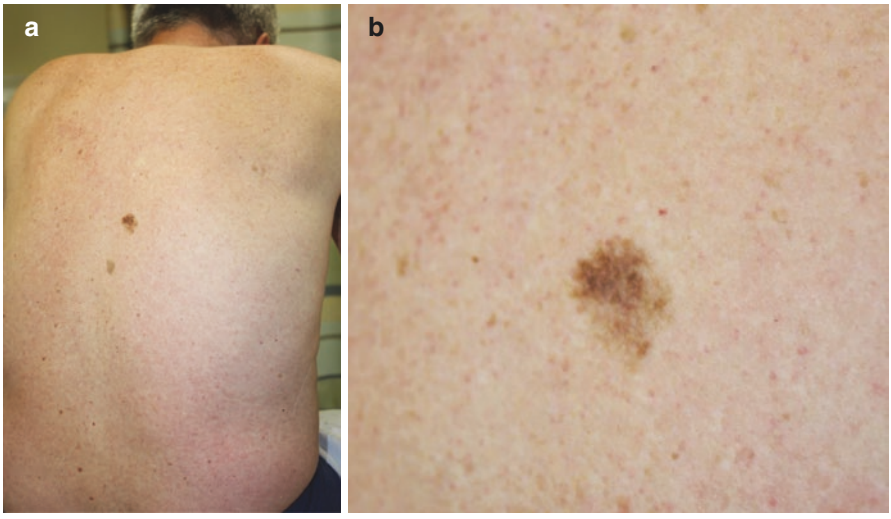

Fig. 22 (**a**) Melanoma in situ presenting on the back of this male patient. Notice the uneven pigmentation and variation in color that stands out in this "ugly duckling". (**b**) Close-up of lesion above. Melanoma in situ. A lack of homogenous pigment and the presence of irregular borders are shown here

brown to gray or black (Fig. 22a–b). With time, SSM may become firmer and thicker as it enters a vertical growth phase. Histologically, atypical melanocytes form and are poorly nested, become confluent along the basal layer of the epidermis, and exhibit "pagetoid" or upward scatter within the epidermis.

Lentigo maligna melanoma (LMM) most commonly affects older patients in the seventh decade of life. It typically presents as a slowly growing, irregularly shaped, light-brown to black macule or patch on sun-damaged facial skin. Lesions can range from a few millimeters to several centimeters in diameter, and borders are frequently ill-defined (Fig. 23). LMM may blend with contiguous benign solar lentigines and surrounding dyspigmented, sun-damaged skin, complicating diagnosis and treatment [39]. Multiple biopsies, which should be interpreted by an experienced dermatopathologist, are frequently required to make a diagnosis. Histologically, LMM shows a proliferation of solitary melanocytes along the basal layer of the epidermis. These subtypes also have a higher propensity to involve skin appendages such as sweat glands and hair follicles.

Nodular melanoma (NM) is characterized by an earlier, more aggressive vertical growth pattern than other subtypes (Fig. 24). It is thought to arise de novo, appears more papular to nodular, and is often firm and surrounded by erythematous induration. It ranges in color from blue to black and can appear ulcerated or hemorrhagic. The incidence of thicker melanomas has remained stable. In recent decades the incidence of in situ and thinner melanomas continues to increase. Although physicians are diagnosing melanomas early, melanoma mortality has not been impacted by this diagnostic trend.

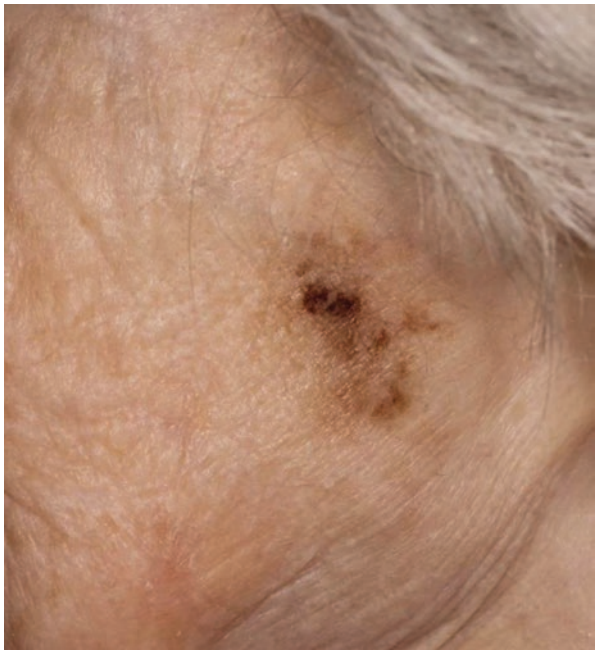

Fig. 23 Lentigo maligna melanoma. This demonstrates the irregular pigmentation and poorly defined borders of a lentigo maligna melanoma

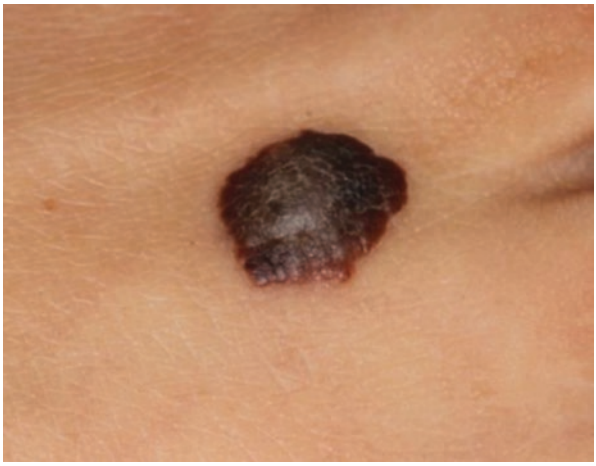

Fig. 24 Nodular melanoma. Note the thickness of this lesion

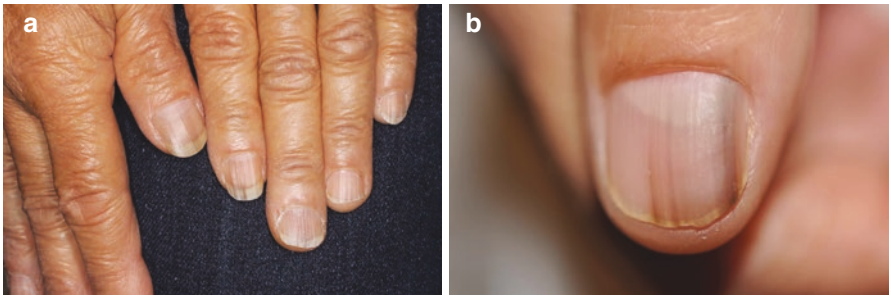

Fig. 25 (**a**) Longitudinal melanonychia is seen in multiple nails, a benign variant seen in more darkly pigmented individuals. (**b**) Note the thicker band of pigmentation and the subtle yet present finding of a Hutchinson's sign on the proximal nail fold. These findings were newly present on a single nail in a Hispanic patient. Nail matrix and nail bed biopsy revealed an invasive melanoma

Acral lentiginous melanoma (ALM) affects the palms, soles, or nail unit. Although a rare variant overall when compared to SSM or LMM, ALM is the most common type of melanoma diagnosed in black and Asian patients [40]. Lesions on the palms and soles typically present as irregularly shaped macules or patches with color variegation from pink to light brown to black. Nail unit disease most commonly presents as pigmented streaks in the nail plate, known as longitudinal melanonychia, with or without discoloration of the proximal nail fold, classically termed Hutchinson's sign. Of note, pigmented longitudinal bands are a normal variant in people with skin of color (Fig. 25a). These are typically light brown and present on multiple nails. A solitary, unusually dark or irregularly shaped band or a thicker band should raise suspicion for melanoma (Fig. 25b). Historically, ALM has been associated with poor prognosis, but this is most likely due to delays in diagnosis and adequate treatment.

Any of the above subtypes may present rarely as an "amelanotic" melanoma, which lacks visible pigment. These lesions are often mistaken for benign moles,

warts, or squamous cell carcinomas. Another rare variant that may lack pigment is desmoplastic melanoma, which typically presents as a firm skin-colored plaque that may be mistaken for scar tissue both clinically and histologically. Mucosal melanomas are extremely rare but may present as pigmented macules or patches on the conjunctiva, in the oral cavity, or on the genitals. Uveal melanoma in its early stages is only detectable by fundoscopic exam and is beyond the scope of this text.

Local signs and symptoms that should raise concern for melanoma are similar to those of other cutaneous malignancies. New, growing, ulcerating, painful, or spontaneously bleeding skin lesions should be evaluated in a timely manner. The "ABCDE" rule, discussed in more detail above, is a fairly sensitive, but non-specific heuristic to aid patients and clinicians in identifying lesions that warrant increased scrutiny. The "ugly duckling" rule, also discussed above, reminds clinicians to pay special attention to pigmented lesions that do not fit an individual patient's common mole pattern. As with SCC, clinical examination of regional lymph nodes near a highly suspicious lesion can be invaluable for identifying metastatic disease and evaluating for recurrence.

Pregnant women frequently seek evaluation for changing moles. One study of 389 pregnant patients found that over 10% of patients reported changes in their moles, most frequently noted during the first trimester. However, no changes in histology were noted on biopsied lesions when compared to a control group [41]. The current consensus is that a suspicious pigmented lesion in a pregnant patient should be treated exactly as it would in a non-pregnant patient. Biopsy or referral to a specialist should not be delayed due to pregnancy. The potential role of estrogen or other hormones in melanoma development is still under investigation, but recent large studies have shown that melanoma prognosis is not significantly affected by pregnancy, nor is there an absolute contraindication to hormonal contraception in females previously diagnosed with melanoma.

Diagnosis and Treatment of Melanoma

Biopsy

Biopsy of a pigmented lesion serves two main purposes: to confirm or exclude a diagnosis of melanoma and to allow for pathologic staging of the tumor, which will in turn guide surgical treatment. The most important prognostic feature is tumor thickness or Breslow depth, but mitotic rate and the presence or absence of ulceration are also included in the seventh edition of the American Joint Committee on Cancer's (AJCC) staging system [42].

A biopsy may sample only part of the lesion ("incisional") or encompass the entire clinically apparent lesion with a small margin of normal skin ("excisional"). In cases of small (less than 1 cm) lesions when suspicion for melanoma is high, an excisional biopsy is recommended with 1–3 mm margins to obtain the entire tumor and accurately assess Breslow depth. Incisional biopsies are typically per-

formed for larger lesions or those in cosmetically or functionally important areas. A punch biopsy tool can be useful both for excisional biopsies of small lesions and to perform several small incisional biopsies within a large lesion concerning for LMM. Shave biopsies are typically reserved for cases where the index of suspicion is low, or the clinician feels confident that adequate depth of the lesion can be obtained. Whatever method is used, the pathologist should be made aware whether a specimen represents the entire clinically apparent tumor or only a sample.

The National Comprehensive Cancer Network (NCCN) does not recommend routine imaging or laboratory tests upon diagnosis of localized melanoma, except to evaluate specific signs or symptoms [38]. Patients with a clinically positive lymph node should have a nodal biopsy and baseline imaging.

Surgical Treatment

Treatment of melanoma is based on AJCC clinical staging criteria and NCCN guidelines [43]. Despite recent advances in medical management of metastatic melanoma, the mainstay of treatment for all stages remains surgical excision when feasible, with margin size dependent upon pathologic stage. Historically, melanoma was excised with aggressive margins of 4 or 5 centimeters or more. However, over time, studies demonstrated that significantly narrower margins did not adversely affect survival [32]. With some notable exceptions, recent studies have confirmed margin recommendations based on expert consensus opinion which have been in place for several decades. For invasive melanoma ≤1.0 mm thick, excision of an additional 1 cm of normal skin around the clinically apparent tumor or biopsy scar is recommended. A 1–2 cm margin is recommended for tumors 1.01–2 mm thick, and a 2 cm margin is recommended for all tumors >2 mm thick. The appropriate excision margin for MIS remains controversial. In general, a 0.5–1.0 cm margin is taken based on expert opinion. Recent literature suggests that a 0.5 centimeter margin may be inadequate for the lentigo maligna subtype most commonly found on the head and neck of elderly patients [44, 45]. Mohs micrographic surgery, aided by immunohistochemical staining, is increasingly being used to treat these ill-defined tumors that in some cases may require >1 cm margins.

The role of sentinel lymph node biopsy (SLNB) in the diagnosis and treatment of melanoma is an area of even greater controversy. Detection of melanoma cells in the lymph nodes draining the primary tumor site is the strongest predictor of overall survival. However, the largest prospective, randomized trial to date of SLNB with or without subsequent complete lymphadenectomy did not show any overall improvement in disease-specific survival [46]. Post-hoc subgroup analysis suggested possible benefits in patients with intermediate-thickness melanoma, but the significance of these findings remains controversial [38]. In general, SLNB is not recommended for tumors ≤0.75 mm in thickness due to an extremely low positivity rate. The

NCCN recommends *consideration* of SLNB for prognostic and staging purposes in patients with tumors 0.76–1.0 mm in thickness with other concerning histologic features or clinical factors, as well as for patients with Stage Ib and II disease. NCCN guidelines also state that patients with known lymph node involvement (Stage III) should be offered a complete lymph node dissection, with the caveat again that a disease-specific survival benefit has not been proven. Lymph node dissection, like all surgical procedures, is not without risk of morbidity. A newly developed genetic expression profile has shown early promise as a non-invasive prognostic indicator and continues to be investigated for its role in determining prognosis and management.

Nonsurgical Treatment

As stated above, surgery is the cornerstone of melanoma treatment. However, topical imiquimod has shown some utility in treating MIS or very thin melanomas arising in elderly patients or other poor surgical candidates. It is also sometimes used as adjuvant treatment for positive peripheral margins in these tumors after incomplete surgical excision. All treatment is off-label, and regimens and outcome data vary widely, but a recent meta-analysis put histologic and clinical clearance rates at 76% and 78%, respectively [47].

Medical and radiation oncologists typically determine adjuvant therapies such as radiation, chemotherapy, and immunotherapy. Historically, cytokine-based immunotherapy such as interferon-α2b played a major role in adjuvant treatment of locally advanced or metastatic disease. The last decade has seen the development of new, more targeted molecular therapies for melanoma. Trials of BRAF kinase inhibitors, anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies, MEK inhibitors, and programmed death receptor signaling PD-L1 antibodies, both alone and in combination, have shown promising, if modest, improvements in survival [48].

Treatment Follow-Up

The NCCN recommends at least annual skin exams for life after the diagnosis of melanoma, with more frequent exams in the first 2–5 years due to an increased risk of recurrence or a new primary tumor during this period. Clinical lymph node examination should be performed at each visit, and patients should be educated about how to perform self-examination. A thorough review of systems should also be performed, with particular focus on those organ systems most commonly affected by melanoma metastases (liver, lungs, bones, brain). Routine follow-up imaging or laboratory evaluation is not recommended for asymptomatic patients with a history of cutaneous melanoma, but can be helpful in monitoring patients with proven metastatic disease.

Other Rare Cutaneous Malignancies

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor of the skin with an aggressive clinical course. About 1500 cases of MCC are diagnosed in the United States each year, and the incidence is rising [2]. It most commonly affects sun-exposed areas, especially the head and neck, on Caucasian patients 70 and older [49]. MCC is believed to arise from neural cells that function as mechanoreceptors within the basal layer of the epidermis. The majority of cases are associated with a novel polyomavirus, known as the Merkel cell polyomavirus (MCPyV), although an exact causative mechanism remains to be fully elucidated [49]. The clinical appearance of primary MCC varies, but tumors are often firm red to purple non-tender papules or nodules (Fig. 26). They can be rock-hard to the touch and may exhibit rapid growth. The head and neck account for almost half of all cases. Eyelids are frequently affected.

The overall 5-year survival for node-negative disease is 64%. This figure drops precipitously to 39% in regional nodal disease and 18% in metastatic disease [50]. Patients who are immunocompromised have an even worse prognosis. Diagnosis requires histological confirmation, and NCCN staging is influenced by tumor diameter, depth of invasion, and lymph node or distant metastasis [51]. Wide local excision with 1–3 cm margins, Mohs micrographic surgery, or other margin-controlled techniques are recommended for local disease. SLNB is recommended for all patients, even those with clinically negative nodes. A positive SLNB is typically followed by complete nodal basin excision and radiation. Adjuvant radiation treatment appears to reduce recurrence of locoregional disease but may not affect overall survival. Platinum-based chemotherapy, with or without etoposide, is generally reserved for widely metastatic disease. Immunotherapies directly targeting the MCPyV or aimed to boost host immune response are currently under investigation [50].

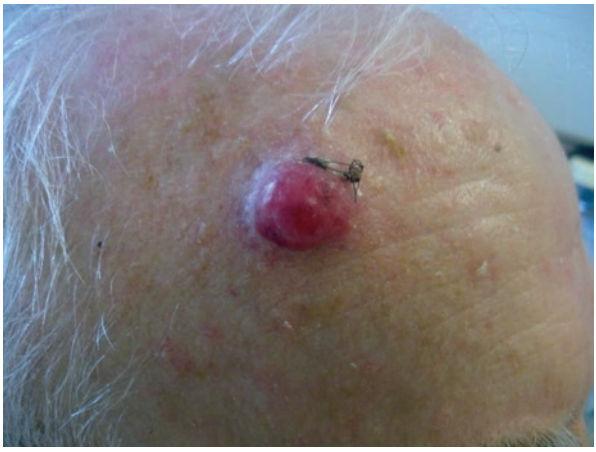

Fig. 26 Merkel cell carcinoma. This neoplasm is red pink due to its vascularity and exophytic and felt firm to palpation

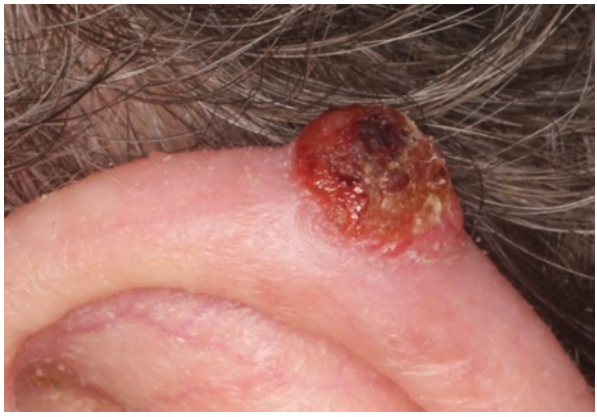

Fig. 27 Sebaceous carcinoma on the helix of the ear

Sebaceous Carcinoma

Sebaceous carcinoma is a rare adnexal neoplasm that tends to occur in areas of high sebaceous gland density. A painless, pink to red or yellowish nodule on the eyelid is the classically described presentation, but other sebaceous areas on the face, scalp, and neck can be affected as well (Fig. 27). The primary lesion, which may also be papular or plaque-like, can resemble a common chalazion, molluscum contagiosum, hemangioma, or keratoacanthoma-type squamous cell carcinoma. A "chalazion" that does not resolve with several weeks of local wound care or antibiotics should raise clinician suspicion for malignancy. Histopathology confirms the diagnosis [52]. A history of extraocular sebaceous carcinoma or multiple sebaceous carcinomas should prompt screening for Muir-Torre syndrome, an autosomal dominant inherited condition associated with increased risk of gastrointestinal and genitourinary malignancies, among others [53].

Cutaneous Metastasis

Roughly 1–2% of all internal malignancies will metastasize to the skin [54]. Cutaneous metastases represent an uncommon occurrence that indicates advanced disease state and portends a poor prognosis. Carcinomas of the lung, colon, and breast are the most likely visceral malignancies to metastasize to the skin. However, melanoma is the most common overall [55]. The scalp, chest, and abdomen are frequently affected. Cutaneous metastases can present as one or multiple nonspecific erythematous, vascular nodules (Fig. 28). The patient may describe bleeding, ulceration, or rapid growth. The first step in managing a suspected cutaneous metastasis is to confirm the cell of origin via biopsy. Treatment aims at identifying and targeting the underlying malignancy, although surgical excision of symptomatic or cosmetically disfiguring metastases may be warranted.

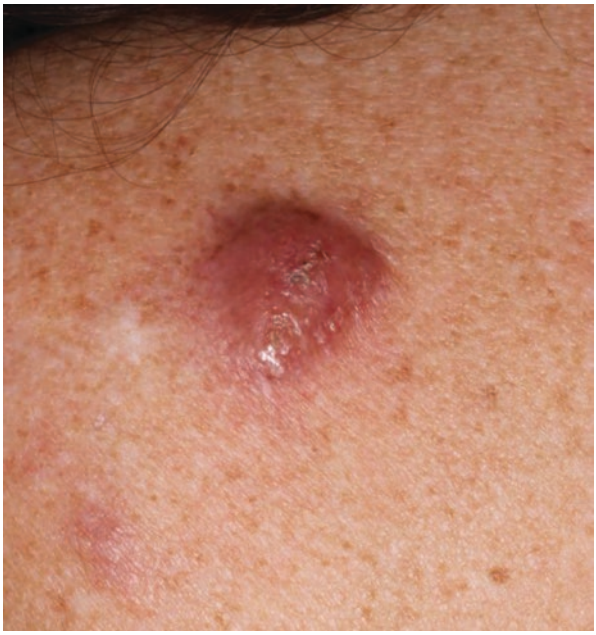

Fig. 28 Cutaneous metastasis. This patient had metastatic breast cancer with a cutaneous metastasis on her upper back

Primary Cutaneous Lymphoma

Primary cutaneous lymphomas are a heterogeneous group of T- and B-cell lymphomas [56]. Mycosis fungoides (MF) and Sézary syndrome (SS) comprise 53% of cutaneous lymphomas and are collectively referred to as cutaneous T-cell lymphomas (CTCL). Early-stage MF typically affects patient in their 50s and 60s and classically presents as well-defined patches and plaques, often with overlying scale, on non-sun-exposed areas (Fig. 29). Plaques may evolve slowly into tumors as the disease progresses. However, MF commonly exhibits clinically indolent behavior and may be managed for years in a manner similar to other chronic papulosquamous diseases such as eczema and psoriasis. Sézary syndrome, a more aggressive leukemic variant, is characterized by circulating neoplastic T cells and erythroderma with or without lymphadenopathy. It can be associated with severe, diffuse pruritus. Although SS often arises de novo over a short time period, some cases have been reported to follow longstanding MF [56].

Primary cutaneous B-cell lymphomas (PCBCL) are less common than CTCL and comprise roughly 20–25% of all primary cutaneous lymphomas [57]. PCBCL also encompasses a heterogeneous group of diseases that are categorized based on histology, immunophenotyping, and prognosis. PCBCL may present as one or multiple patches, plaques, nodules, or firm tumors. In most cases, the disease remains localized to the skin. In general, PCBCL has a more indolent clinical course and favorable prognosis as compared to nodal disease [58].

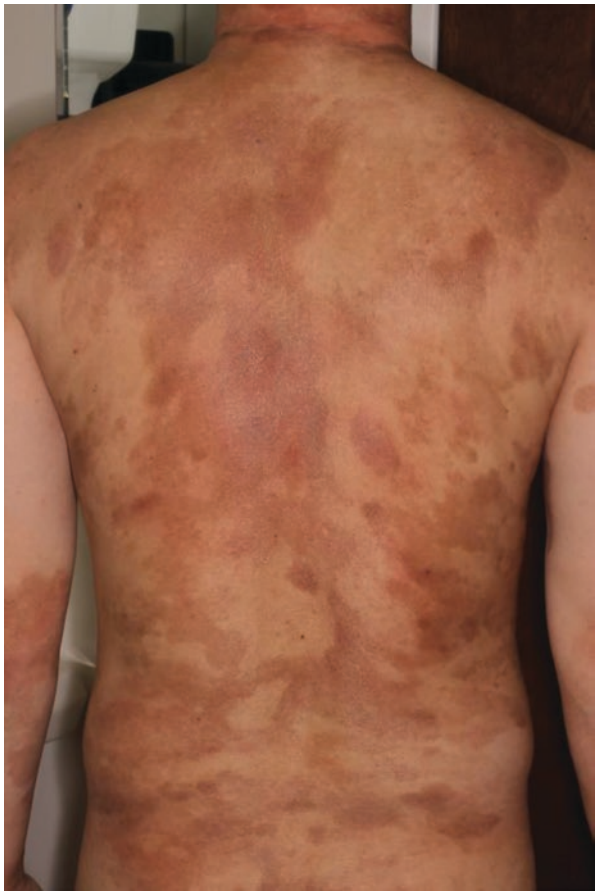

Fig. 29 Mycosis fungoides manifesting as asymmetric erythematous plaques

Proper diagnosis, classification, and staging of primary cutaneous lymphomas often require a battery of tissue- and blood-based tests, imaging studies, and lymph node sampling. Patients should be referred to a cutaneous lymphoma specialist for disease management and surveillance.

Dermatofibrosarcoma Protuberans (DFSP)

DFSP is a low-grade soft tissue malignancy that typically arises in younger patients aged 24–50 years. It most commonly occurs on the trunk, with a predilection for the shoulder or pelvic region, but may also present on the head and neck. It appears as a painless, slowly enlarging skin-colored to pink or red subcutaneous nodule or plaque (Fig. 30a–b). Lesions are often firm to the touch and feel adherent to underlying structures. The diagnosis is made based on histology and immunohistochemistry.

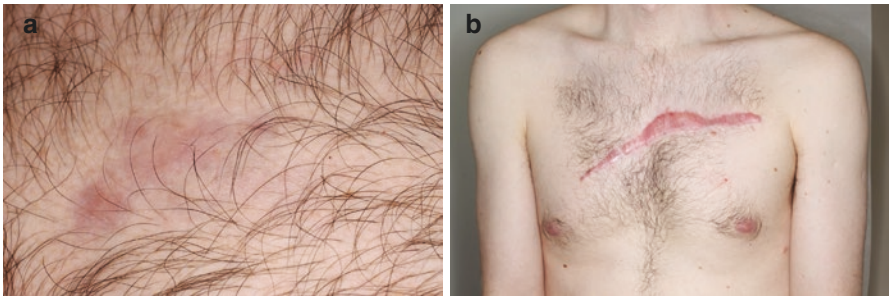

Fig. 30 Dermatofibroma sarcoma protuberans. (**a**) This shows an ill-defined sclerotic firm pink plaque. As these lesions progress, they can become more raised and nodular in appearance as described in more classical cases. (**b**) A large scar results from the reconstruction required after excision by Mohs micrographic surgery

DFSP has a tendency to recur after treatment, but the rate of distant metastasis is very low [59]. The standard of treatment is wide local excision to the underlying fascia or Mohs micrographic surgery. The chromosomal translocation t(17;22) q(22;q13), also found in chronic myeloid leukemia, is thought to play a pathogenic role in a majority of cases. Imatinib maculate targets the platelet-derived growth factor receptor activated by the translocation and is FDA-approved for patients with unresectable recurrent, or metastatic DFSP.

Angiosarcoma

Angiosarcomas are rare, aggressive tumors of vascular or lymphatic origin. Early lesions can be very subtle, initially resembling a bruise, but they tend to progress to nodules or tumors which ulcerate and hemorrhage. Angiosarcoma most commonly presents on the face or scalp in elderly men [60]. Most cases are sporadic, but disease presenting in non-head and neck locations is often associated with chronic lymphedema or a history of radiation, with peak incidence 5–10 years after radiation [61]. Treatment entails surgical resection and adjuvant radiation; recurrence is high.

Mammary and Extramammary Paget's Disease

Mammary Paget's disease most commonly presents in postmenopausal women in conjunction with an underlying intraductal breast carcinoma. It typically appears as a scaly pink to red plaque involving the nipple. Mammary Paget's disease often mimics an eczematous dermatitis, which can lead to delays in diagnosis. Patients classically provide a history of "eczema" of the nipple or breast

that has not responded to topical corticosteroids of increasing strength. Benign dermatitides of the nipple are fairly common, but a clinician should always ensure that a patient is up-to-date on age-appropriate mammography screening, particularly when the presentation is unilateral. Needless to say, a biopsy-proven diagnosis of mammary Paget's necessitates further investigation for underlying malignancy.

Extramammary Paget's disease is frequently divided into two subtypes: primary and secondary. Primary extramammary Paget's, the more common form, is an intraepithelial adenocarcinoma that arises de novo in apocrine gland-bearing skin such as the vulva, perianal region, scrotum, penis, or axillae. Surgical excision or Mohs micrographic surgery is the standard of care, but recurrence is common. Secondary disease is thought to represent contiguous spread of an underlying malignancy, typically localized to the same anatomic region [62, 63].

Patient Education

Comprehensive patient education includes skin cancer prevention and detection strategies and applies to all patients, regardless of age or skin type. Although melanoma and NMSC are far more common in whites, darker-skinned patients tend to present at more advanced stages with poorer prognosis [64]. The American Academy of Dermatology recommends year-round, everyday application of a broad-spectrum (UVA- and UVB-blocking), water-resistant sunscreen with an SPF of at least 30 for all skin types. A sufficiently thick layer should be applied to all uncovered skin 15 minutes prior to sun exposure and reapplied every 2 hours while outdoors thereafter (or every hour if swimming or sweating). Sun protective clothing and avoidance of peak sun hours between 10 am and 2 pm further reduce carcinogenic UV exposure. Tree or cloud shade is not sufficiently protective. Fair skin, severe or blistering sunburns, and prolonged chronic sun exposure are all associated with increased risk of skin cancer [20]. Tanning bed use has been associated with both melanoma and NMSC and should be strongly discouraged.

Conclusion and Future Directions

As our population ages, the incidence of skin cancer and its associated healthcare costs are projected to increase. Improved patient education, prevention, early detection, and treatment strategies are all needed to counter these trends. With the shift toward an accountable care organization model, primary care doctors and specialists alike will be expected to contain costs while improving quality and access to care. Technology, in the form of electronic medical records, telemedicine, and other nascent or as yet unconceived innovations, will play an increasingly important role

in this process. Developments in genetics and targeted molecular-based therapies are beginning to change the diagnosis and treatment of melanoma, still one of the deadliest human cancers. As our basic understanding of tumor biology grows, so too will our ability to alleviate the significant toll skin cancer takes on our patients' lives.

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Rosacea

Edward F. Ryan Jr.

Rosacea is a chronic inflammatory disease primarily involving the centrofacial skin. The National Rosacea Society has estimated that approximately 16 million Americans are affected by this disease. The prevalence is likely to be underestimated in clinic-based population studies where selection bias may play a role, and when observations are made by direct observation of the population, the number of patients with rosacea is often higher than study-based estimates. It is twice as common as psoriasis which is estimated to affect 7.5 million people in the USA [1–3]. This disease results in significant quality of life issues, and there have been numerous studies documenting this. Rosacea patients have a higher incidence of depression, anxiety, and embarrassment [4]. There have been multiple studies which report an improvement in the quality of life scores after treatment for various aspects of rosacea [5–7].

In 2002, a classification system was proposed by the National Rosacea Society Expert Committee [8]. Prior to this, patients with rosacea were recognized because they presented with flushing, redness, and acneiform papules on the face. The Expert Committee proposed the following four subtypes of rosacea: Subtype 1, erythematotelangiectatic rosacea (Fig. 1); Subtype 2, papulopustular rosacea (Figs. 2 and 3); Subtype 3, phymatous rosacea (Fig. 4); and Subtype 4, ocular rosacea. The progression from one subtype to another is controversial. A recent paper did report a small percentage of patients who did progress from one subtype to another, but the natural history of rosacea is unknown [9]. Subtype 1 is the most common, followed by Subtype 2 [10]. There is often overlap between the various subtypes [11].

Rosacea occurs most commonly in adults older than 30 and is two to three times more prevalent in females than males. Rosacea patients often report flushing, stinging, burning, dryness, and scaling. Physical findings include centro-

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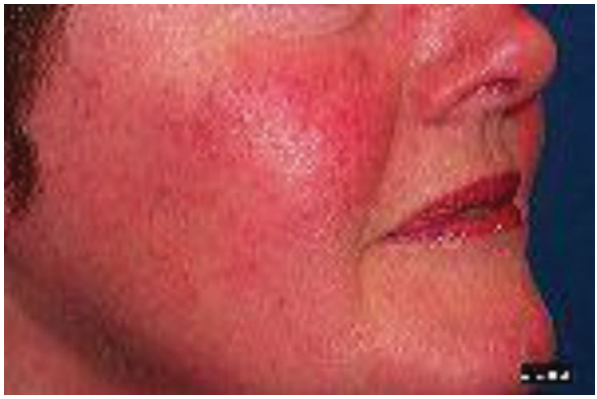

Fig. 1 Subtype 1 – erythematotelangiectatic rosacea. (Derm Net NZ.org)

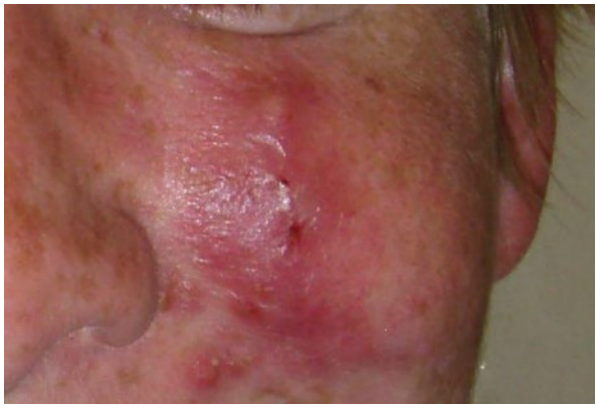

Fig. 2 Subtype 2 – papulopustular rosacea. (Derm Net NZ.org)

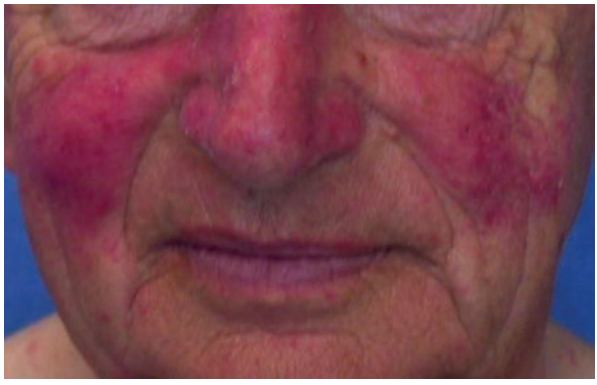

Fig. 3 Subtype 2 – papulopustular rosacea. (Derm Net NZ.org)

facial erythema, inflammatory papules, pustules, telangiectasias, and flushing. Erythematotelangiectatic rosacea presents with transient flushing and persistent erythema on the malar regions. Papulopustular rosacea is distinguished by inflammatory papules and pustules on the central face. Phymatous rosacea is characterized by thickened skin with sebaceous hyperplasia and surface irregularities and

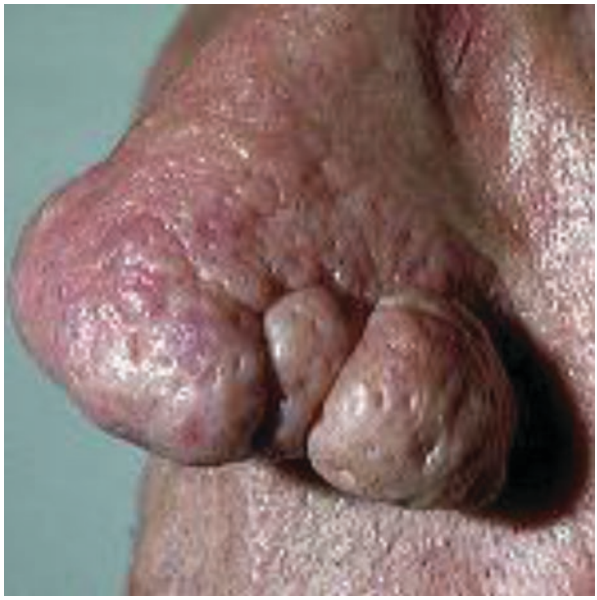

Fig. 4 Subtype 3 – rhinophyma. (Derm Net NZ.org)

most commonly affects the nose although it can be seen on the chin, cheeks, and forehead. Males are more commonly affected by phymatous rosacea [11]. Ocular rosacea can present with various findings including blepharitis, conjunctivitis, chalazion, and eyelid erythema. This can present after a patient already has cutaneous disease or in about 20% of cases occurs as the initial manifestation of rosacea [12].

Skin biopsy is often non-specific and is not generally indicated to make the diagnosis of rosacea. It is sometimes necessary when the diagnosis is unclear and other problem needs to be ruled out.

The differential diagnosis includes acne vulgaris, cutaneous or systemic lupus, carcinoid syndrome, seborrheic dermatitis, steroid rosacea, lupus pernio (sarcoidosis), demodicidosis, gram-negative folliculitis, perioral dermatitis, actinic damage, and rarely cutaneous B cell lymphoma [13].

The cause of rosacea is not clear. It is a chronic inflammatory disorder with multiple underlying abnormalities. Rosacea patients have been found to have dysregulation of the innate immune system. There is an increase in cathelicidin, an antimicrobial peptide, along with an increased amount of kallikrein which is a serine protease responsible for conversion of cathelicidin into LL-37, it's active form. There is also an increase in Toll-like receptor 2. Matrix metalloproteinases, which convert prekallikrein to kallikrein, are upregulated. Ultraviolet light plays a role causing productions of reactive oxygen species (ROS) which can stimulate TLR-2 and further inflammatory mediators such as cathelicidin [11].

In addition there is some debate about the role of *Demodex*, a saprophytic organism which is found in increased numbers in the skin of patients with rosacea and can stimulate Toll-like receptor 2. This organism also harbors *Bacillus oleronius*, a gram-negative bacteria, which can stimulate increased production of TNF, MMP-9, and interleukin-8 [14].

Finally, neurogenic dysfunction is noted, and stimuli such as spicy foods, alcohol, and heat or cold can stimulate transient receptor potential channels (TRPs) such as TRPV1 and TRPA1. This results in release of substance P and resultant inflammation [15].

The net effect of the above is an inflammatory cascade resulting in inflammation, erythema, vasodilatation, and tissue remodeling.

In addition to the chronic inflammation, all rosacea patients have abnormal barrier function. There is increased trans-epidermal water loss (TEWL) and an abnormal lactic acid stinging test which also measures skin barrier function [16, 17].

Rosacea is often worsened by certain trigger factors. These would include caffeinated beverages, spicy foods, sunlight, heat, cold stress, and strenuous exercise [18, 19]. Given the abnormal skin barrier and heightened sensitivity, care should be taken to ensure that the patient uses mild soaps and cleansers and broad spectrum sunscreens. This must be discussed when reviewing the diagnosis and proper treatment during the office visit.

Treatment of rosacea requires a review of the physical findings, characterization of subtype, pathogenesis, therapeutic options, and expected response to the selected choice of treatment. The current interventions available for use would include the following topical agents: metronidazole, azelaic acid, and ivermectin. These topical agents are all approved for the treatment of type 2 papulopustular rosacea, and there is moderate- to high-quality evidence for the efficacy of these three agents [20]. Oral antibiotics including doxycycline and minocycline are effective for the treatment of inflammatory lesions of rosacea. Sub-antimicrobial-dose doxycycline (40 mg immediate release and 10 mg delayed release) has also been shown to be effective and does not alter the microbial flora as full-dose antibiotics do.

Dermatologists represent 1% of physicians but prescribe 5% of antibiotics. This contributes to increasing bacterial resistance [21]. It is incumbent upon the dermatology community to limit the use of antibiotics to decrease bacterial resistance and preserve the efficacy of our current antibiotics. Sub-antimicrobial-dose doxycycline had no effects on antimicrobial resistance in a 9-month study [22]. Treatment can consist of topical therapy with one of the above noted agents, oral therapy, or a combination of the two. Patients should be advised that it generally takes 8–12 weeks of continuous therapy to see optimal results.

Erythematotelangiectatic rosacea or ETR is not effectively treated with any of the topical therapies or antibiotics already discussed. There are two agents available for treatment of this subtype: topical brimonidine tartrate and oxymetazoline hydrochloride (HCL). These are both alpha-adrenergic agonists producing vasoconstriction of abnormally dilated facial vessels. The therapeutic effect is transient lasting up to 12 hours.

Treatment of redness and telangiectasias can also be accomplished with different laser and light sources including but not limited to IPL (intense pulsed light) and pulsed dye lasers.

Rosacea has a tendency to recur, and treatment is often necessary over a prolonged period of time. Patients should be seen intermittently while using the medications described above in order to assess response to these agents and decide on the future direction of their therapy.

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Skin Conditions in Athletes

Susan K. Fidler, Lauren Inners, and Ilana Zeises

Skin conditions are a common concern for athletes as they can be painful and contagious and result in time away from sports participation. Given the close contact among athletes, the spread of contagious skin conditions is of particular concern. Common infectious skin conditions from bacterial, fungal, and viral sources are often transmitted between athletes. Among skin conditions in high school athletes, about 60% are from bacterial skin infections, and 28% are from tinea infections. The infections are most common in wrestling and football and most often occur in the head and neck region [1]. Prompt recognition, treatment, and removal from play until the infection risk is mitigated are important considerations for athletes. Additionally, athletes are prone to other mechanical dermatoses related to repetitive activities and intense training. These are important to recognize as noninfectious and provide symptomatic and supportive treatment to allow athletes to continue training through these self-limited, but oftentimes bothersome, skin conditions.

Infectious Dermatoses: Diagnosis, Treatment, and Return-to-Play Considerations

Infectious skin dermatoses are very common in athletes, especially those who are involved in close contact activities like wrestling or football. In wrestling, 8.5% of all high school and 20.9% of all collegiate athletic injuries were due to skin

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infections [2]. Quickly diagnosing infectious dermatoses and removing the athlete from participation help decrease spread. Initiating early treatment expedites return to participation. In general, return to play of athletes with infectious dermatoses is determined by the National Collegiate Athletic Association (NCAA) [3] and the National Federation of State High School Associations (NFHS) wrestling guidelines [4].

Bacterial Infections: Abscesses, Furuncles, Cellulitis, Folliculitis, and Impetigo

Furuncles and abscesses are common, erythematous, and fluctuant soft tissue masses (see chapter on "Bacterial Skin Infections") (Fig. 1). The mainstay of treatment is aimed at incision and drainage of the purulent collection. In an athlete, a culture of these wounds to assess for methicillin-resistant *Staphylococcus aureus* (MRSA) is encouraged. In typical practice, abscesses without cellulitis are treated with incision and drainage, and antibiotics are not always prescribed. However, it is important to note that return-to-play criteria for all bacterial skin conditions for both NCAA and NFHS require the athletes to be on oral antibiotics.

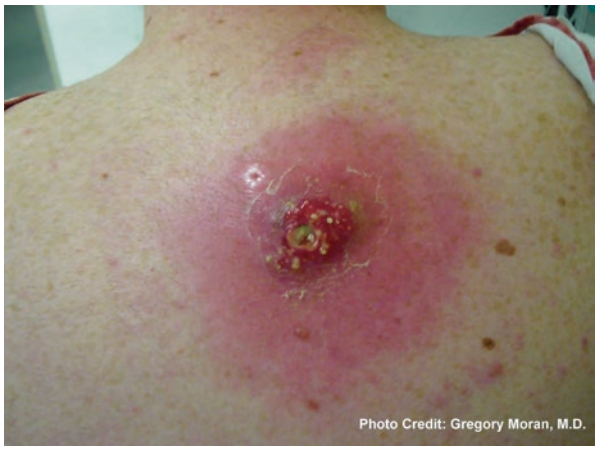


Fig. 1 MRSA skin abscess. (Greg Moran, CDC)

Community-Acquired Methicillin-Resistant Staphylococcus aureus (MRSA)

A specific area of concern is the athletic associated skin and soft tissue infection due to MRSA (see chapter on "Bacterial Skin Infections"). Risk factors for MRSA specific to athletics include body shaving, towel sharing, turf burn, open abrasions, and close contact in practice and competition. [5, 6] MRSA is very common in athletic spaces. Nasal colonization for MRSA in athletes on average is about 6%, up to 8% in the United States, and up to 13% in collegiate athletes (double that of a typical intensive care unit patient). MRSA prevalence in athletes has been reported to be 23% depending on the sport and the time of the season. [7, 8] For athletes with evidence of colonization, their risk of skin infection in the following 3 months was more than seven times higher than those who were not colonized. In a study examining the surfaces of ten high school athletic training rooms and locker rooms, 47% of all surfaces tested were positive for MRSA [9]. Collegiate sports with the highest prevalence for MRSA are wrestling, football, and basketball, but it can certainly be seen in any other sport [8].

Sports-related MRSA infection usually presents as an abscess with surrounding cellulitis and with pain out of proportion to exam. Abscess is the most common presentation found in well over half of all cases of sports-related MRSA infection [10]. The treatment for MRSA is generally incision and drainage plus a systemic antibiotic agent based upon culture results.

Athletes with MRSA lesions should be held from both practice and competitions until the lesions are healed or can be covered adequately. As per the NCAA, adequately covered is defined as "the noninfectious/noncontagious lesion is covered by a gas impermeable dressing, pre-wrap and stretch tape that is appropriately anchored and cannot be dislodged throughout the sport activity." [3] Athletes should be instructed to wash their hands with soap and water after touching the bandage. At the collegiate level, the NCAA has developed regulations in certain sports such as wrestling regarding the banning of infected players from competition. Wrestlers must remain free of new lesions for 48 hours, complete at least 72 hours of antibiotic therapy, and remain free of any purulent lesions.

Prevention should be encouraged through having good hand hygiene; showering immediately after activities; avoiding common whirlpools with skin abrasions or infections; avoiding sharing personal hygiene products such as towels, soap, and daily athletic gear; educating athletes and coaches regarding infectious skin conditions; and having good coverage of all infectious skin lesions until fully healed. The Centers for Disease Control and Prevention (CDC) also gives guidance for facility care for locker rooms and athletic training rooms [11]. Eradication and decolonization are controversial topics. Decolonization has been shown to be effective at eradicating MRSA colonization in the short term (<10 days after treatment) but only decreases the risk of infection by about one-third over 3 months and does not prevent recolonization [8].

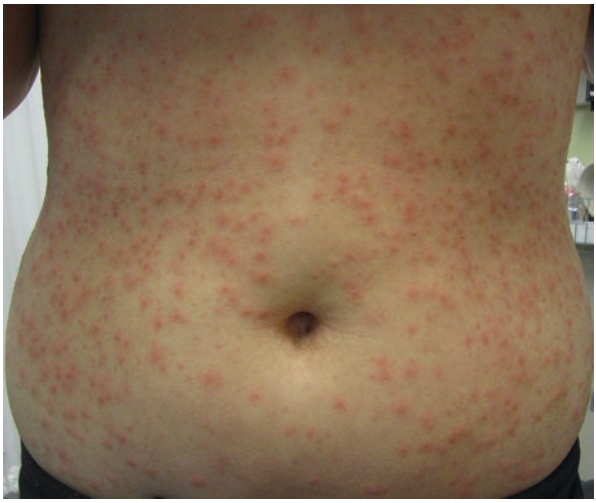


Fig. 2 Hot tub folliculitis. (Wikimedia Commons with permission from James Heilman, MD)

Athletes are at particular risk of other superficial skin infections like cellulitis, folliculitis, and impetigo. This can be due to multiple reasons such as skin trauma, heat and humidity, and poor hygiene. *Pseudomonas* folliculitis is frequently linked to under-chlorinated hot tubs and swimming pools (Fig. 2). Impetigo is very easily spread from person to person. The yellow "honey-colored" lesions and crusts are most commonly noted on the face, neck, and upper extremities. Often impetigo may be self-limited or cleared with topical therapy, but the NFHS references oral antibiotic therapy in order to return to play (Fig. 3). For return to participation, athletes must have completed 72 hours of oral antibiotics. There must be no new skin lesions within the past 48 hours, and all lesions must be free of moisture, exudate, or drainage. They cannot participate unless all criteria are met, even if the lesion is covered [3, 4].

Viral Infections: Herpes, Molluscum, and Warts

Herpes gladiatorum (HG) is caused by herpes simplex virus type 1 (HSV-1) and presents as a typical HSV infection of clustered vesicles on an erythematous base (Figs. 4 and 5). HG accounts for a significant amount of contagious dermatoses in athletics and is transmitted via skin-to-skin contact. The likelihood of contracting herpes after sparring with an infected partner is about 33%. Nearly three-quarters of HG is found in the head and face, with the right side being more common due to the prevalence of right-hand dominance [12]. Lesions may also involve the eye, causing conjunctivitis and prompting referral to ophthalmology. There is typically an incubation period of 2–20 days after exposure to the virus. During the incubation period, athletes may experience prodromal symptoms including fever, lymphadenopathy, fatigue, myalgias, and headache. The lesions crust over within a few days and then take up to 2–3 weeks to heal completely. Treatment is with an oral antiviral medication.

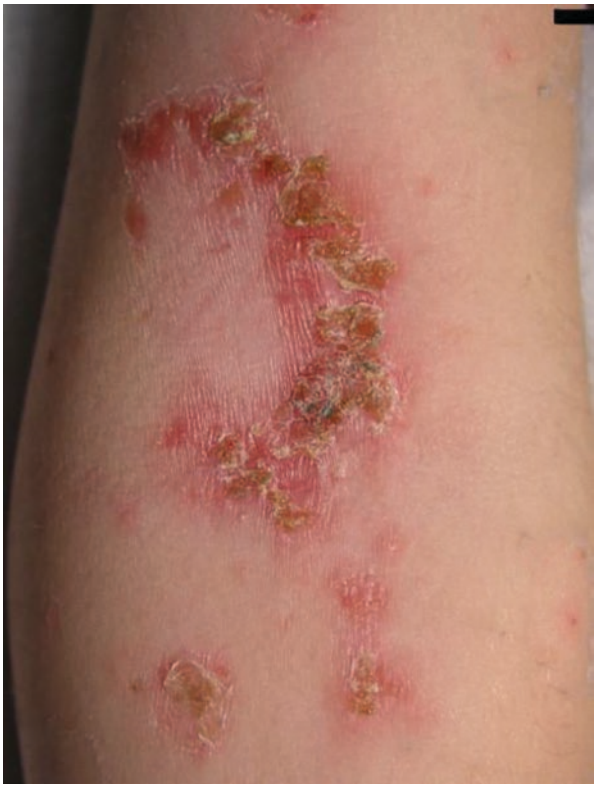
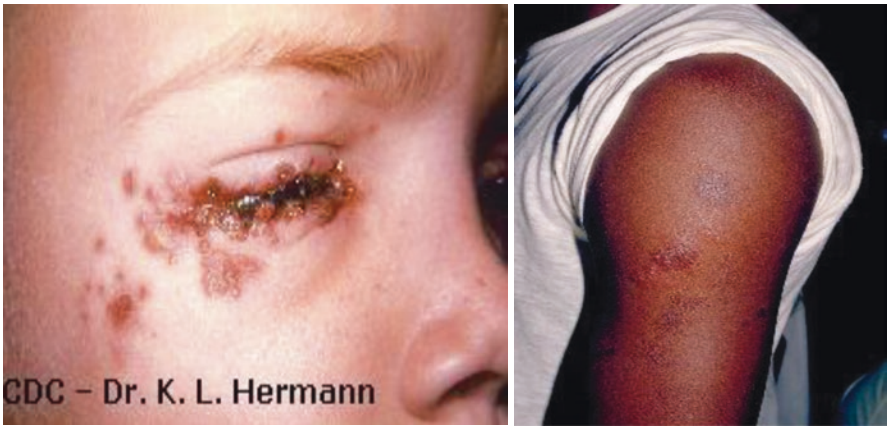


Fig. 3 Impetigo elbow. (CDC)



Figs. 4 and 5 Herpes gladiatorum. (CDC—KL Herman/Allen W Mathies)

Due to the highly contagious nature of infections, prevention of spread is of utmost importance. The NFHS recommends that any athletes in contact with an infected individual in the 3 days prior to onset be isolated from close-contact activities for 8 days and reexamined daily. Prevention with antiviral therapy can be considered. In a 10-year study at a wrestling camp, prophylactic antiviral treatment,

regardless of HSV serologic status, decreased the rate of HG occurrence by 85% [13]. Serologic screening for HSV-1 could be considered in determining suppressive therapy during the season [12].

For all forms of herpes infection (including HG, labialis, zoster, whitlow, etc.), athletes may not return to play until all lesions have "firm adherent crust" and there are no remaining vesicles or drainage. NCAA and NFHS differ slightly in other return-to-play criteria. NFHS requires 10 days of antiviral treatment for primary outbreaks and 14 days if systemic symptoms are present. Recurrent outbreaks require 120 hours (5 days) of oral therapy and no new lesions since the onset of therapy. NCAA required 120 hours of oral therapy, no systemic symptoms, and no new lesions for 72 hours. Active lesion may not be covered to allow participation [3, 4].

Molluscum contagiosum is a skin infection caused by a virus from the *Poxviridae* family (Fig. 6). Lesions consist of umbilicated papules that are white to skin colored and are 3–5 mm in diameter (see chapter on "Warts and Molluscum"). Molluscum is more likely to be found in children and commonly found in swimmers, gymnasts, and wrestlers. The papules are usually asymptomatic. Lesions spread through skin-to-skin contact and so should be covered during contact sports. The infection is self-limited but can take months to years to resolve without treatment. The most common treatments for molluscum are liquid nitrogen and curettage. Treatments prevent the spread of lesions on the athletes' body and to other athletes.

Athletes with molluscum must have lesions covered and may be required to have treatment prior to returning to play. Wrestlers may not compete with this condition, as the NCAA requires athletes to have lesions curetted or removed prior to resuming competition. The NCAA only accepts lesions on the trunk or upper thigh, which are covered by clothing, to have adequate coverage. The NCAA also states that solitary, localized, or clustered lesions can be covered with "a gas impermeable dressing, pre-wrap, and stretch tape that cannot be dislodged." [3]

Warts are also spread via skin-to-skin contact (Fig. 7). The infections are caused by human papillomavirus; they present as small, skin-colored, firm papules, often on the hands and feet, and can be painful. Warts can be differentiated

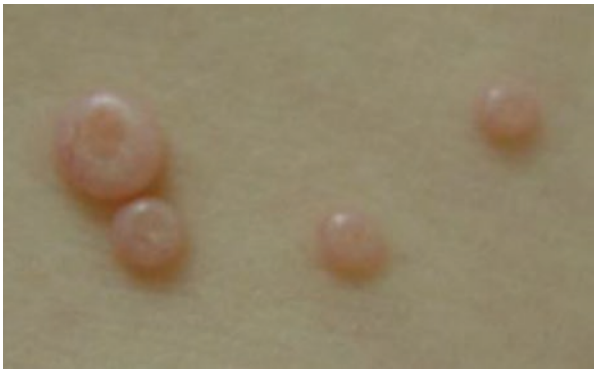


Fig. 6 Molluscum contagiosum. (CDC—Dave Bray, MD, Walter Reed Army Medical Center)

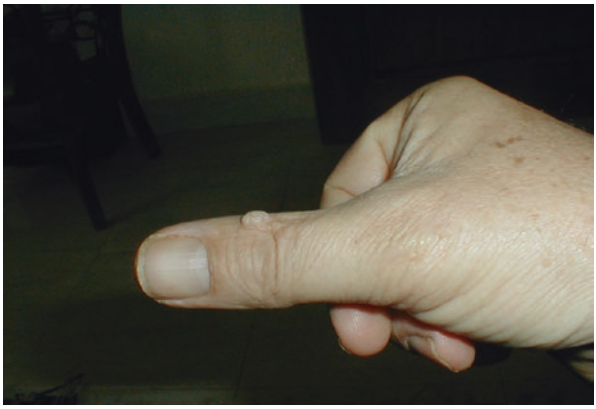


Fig. 7 Common warts. (By Lucien Mahin—Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=15168704)

from corns and calluses. When warts have their overlying hyperkeratotic material removed, they will have an underlying pericapillary hemorrhage (black spots), whereas calluses will have nothing present, and corns will have a central core. Removal of warts can be done through many methods (see chapter on "Warts"). Athletes may return to play after curettage or may participate if the warts are covered [3, 4].

Fungal Skin Infections

Tinea infections with *Trichophyton rubrum or tonsurans* are most common in athletes. The location of the tinea infection determines the treatment course and return-to-play considerations (see chapter on "Tinea"). Both the NCAA and NFHS state that tinea capitis must have 14 days of oral treatment prior to return to play. Tinea corporis must be treated with >72 hours of topical therapy and be adequately covered for return to play. Prophylaxis with antifungal medication can be considered and has been shown to reduce incidence of tinea infections to close to zero. One study occurring over a 10-year period found that in wrestlers, fluconazole 100 mg for 3 days at the start of the season and repeated 6 weeks into the season was effective for prophylaxis with no reported adverse effects [14].

Tinea pedis, or athlete's foot, is a dermatologic condition that occurs in 70% of the population. The prevalence of tinea pedis in an athletic population has been documented to be about two times higher than the general population [15]. The most common dermatophytic causes of the infection are *Trichophyton rubrum* and *Trichophyton mentagrophytes.* Tinea pedis can be classified into three different categories based upon the location and the appearance of the infection. Interdigital tinea pedis is the most common type. The lesions are often scaling, erythematous plaques (Fig. 8). As the infection progresses, the skin can become macerated, and fissuring can occur resulting in superinfection with both gram-positive and gram-negative bacteria. The moccasin subtype is often a chronic

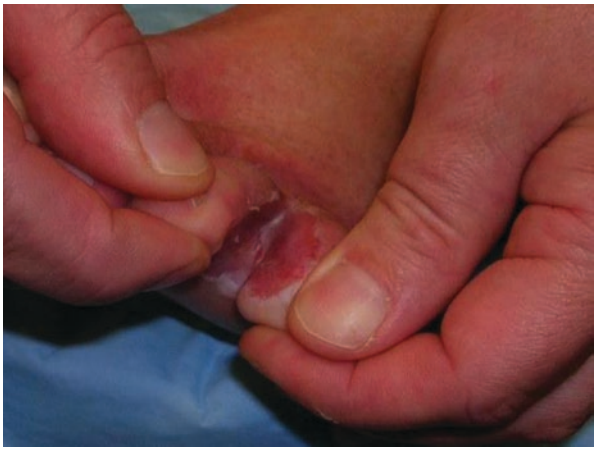


Fig. 8 Tinea Pedis. (Jefferson Clinical Images Database. http://jeffline.jefferson.edu/JCI/. Accessed [June 22, 2016])

infection that results in fine, scaling, erythematous plaques that are located on the heels, soles, and lateral aspects of the feet. The third subtype is the vesiculobullous type, which consists of vesicular and bullous lesions filled with clear fluid. This typically presents on the instep of the sole and can be very pruritic. It may present in conjunction with a bacterial superinfection with *Staphylococcus aureus* or group A *streptococcus*. One thing all three subtypes have in common is that they spare the dorsum of the feet. A prolonged course of treatment of up to 4–6 weeks is recommended for tinea pedis. Prevention is encouraged through using synthetic socks, keeping feet dry, and wearing sandals at all times in the locker rooms and showers [16]. There are no participation restrictions in athletes with tinea pedis infections.

Blisters

Blisters are a dermatological condition caused by the friction of skin rubbing against another surface causing the epidermal cells to split apart from one another, creating a pocket filled with transudative fluid (Fig. 9). The healing of a blister may be rapid if further frictional forces are avoided. Within the first 6 hours, the fluid begins to reabsorb, and by day 2 new cells begin to generate. In general, blisters <5 mm should be managed conservatively with activity modification when possible and protective padding like moleskin. Blisters larger than 5 mm may be drained with sterile technique after 24 hours, leaving the protective "roof" intact [17].

Numerous studies have looked at options for prevention. In general, appropriate footwear, keeping skin dry, and "foot hardening" through a slow increase in time spent in new footwear are recommended. Specific studies have looked at the use of acrylic socks, the application of Drysol, specific shoe inserts, bandages, and foot taping to prevent blisters all with some reported efficacy [18, 19].

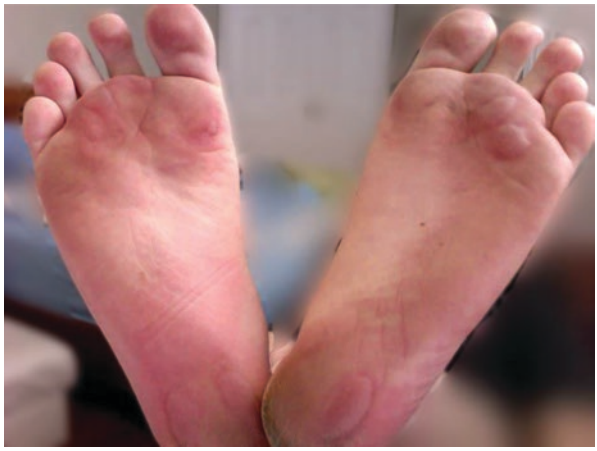


Fig. 9 Friction blister. (Wikimedia Commons—Andry French)

Other Self-Limiting Sports-Specific Dermatoses [20–24]

All of the below dermatoses are self-limiting, and athletes are able to return to play when tolerated.

	Diagnosis	Treatment	Prevention
Acne mechanica	Acne occurring due to friction, heat, or occlusion from protective equipment such as chinstrap or shoulder pads	Traditional acne therapies	Immediately showering after activity, moisture-wicking clothing
Tennis toe	Subungual hematoma due to repetitive trauma	Consider nail trephination if pain is acute or severe	Properly fitting footwear, shoe stretching, trimming toenails
Talon noir	Calcaneal petechiae due to intraepidermal bleeding from shearing forces presenting as black macules, often confused for melanoma, common in young basketball players	None. Confirmed diagnosis with excision revealing the hemorrhage	
Jogger's nipples	Abrasive nipple injury due to rubbing of the nipple on tight fitting clothing. Worsened by cold air or direct stimulation	Treat as a skin abrasion with good hygiene, antibiotic ointment, and bandages	Properly fitting clothing. They may use lubricants or bandages during exercise
Runner's rump	Small ecchymoses found in the upper gluteal cleft of distance runners caused by constant friction when running	None	None

	Diagnosis	Treatment	Prevention
Swimmer's xerosis	Dry skin in swimmers. The naturally protective skin sebum is destroyed by the chlorine and leads to moisture loss, resulting in a dry, scaly, itchy skin. This can be exacerbated when using hot showers and soaking in hot tubs	Moisturizing after swimming	Athletes should quickly rinse off in cool water after swimming
Golfer's nails	Splinter hemorrhages or linear dark streaks in the fingernails seen in golfers who grip the club tightly		
Surfer's nodules	Nontender, fibrotic nodules on the pretibial surface of the leg or the mid-dorsum of the foot. They occur most frequently over bony prominences and are likely a result of repetitive contact between the surfboard and the bone or possibly a foreign body reaction to sand or other foreign materials	Athletes may use protective padding on knees and ankles	Nodules may be treated with topical keratolytics, such as salicylic acid and lactic acid. Other options include intralesional steroids, topical steroids, and surgical excision
Piezogenic papules	Skin-colored or yellowish occasionally painful papules along the lateral plantar surface of the heels. They may become obvious upon prolonged standing or exercise. They are caused by herniation of subcutaneous fat through small tears in the plantar fascia	Elevation of the feet often provides relief. Although no successful treatment has been found, heel cups inserted into shoes can often alleviate the discomfort during exercise	

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Gynecologic Dermatology

Priscilla Sepe and Amy Clouse

Genitourinary Syndrome of Menopause

The term genitourinary syndrome of menopause (GSM) was coined in 2013 by the International Society for the Study of Women's Sexual Health to replace the terms vulvovaginal atrophy and atrophic vaginitis [1]. The latter terms fell into disfavor for a number of reasons, including the lack of inclusion of urinary symptoms, the pejorative implication of the word "atrophy" for postmenopausal women, and the lack of a state of inflammation or infection, which is implied by the term "vaginitis."

Epidemiology

In the United States, the median age of menopause is 51 years [2]. The North American Menopause Society estimates that 10–40% of women will experience at least one symptom of GSM [2]. While vasomotor symptoms tend to abate with time, genitourinary symptoms are generally chronic and progressive, with increasing severity with advances in age.

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Pathophysiology

After menopause, circulating levels of estrogen and progesterone are lower, and this affects the vulva, vagina, urethra, and bladder trigone where there are high concentrations of estrogen receptors [1]. This leads to fewer blood vessels and decreased elastin and collagen content of the vaginal walls [1, 3]. As the vaginal epithelial tissue thins, it becomes less flexible and more friable [3]. Superficial epithelial cells are replaced with parabasal cells – small, round cells with large nuclei – that are markers of GSM. As vaginal pH increases, the normal microbiome shifts with a decrease in lactobacilli and the susceptibility to pathogens increases [3].

Symptoms

Vulvovaginal dryness, irritation, and itching are common in GSM. Sexual symptoms stem from decreased lubrication during sexual activity and the thinning of epithelial tissues which can lead to bleeding after intercourse. Dyspareunia is common, with a third of postmenopausal women avoiding sexual activity because of associated pain [3]. Discomfort may be present in the absence of sexual activity and may be brought on by tight-fitting clothes, sitting, or exercising [4]. Urinary symptoms include dysuria, urgency, and recurrent urinary tract infections.

Clinical Features

Typical appearance is of thin, dry pale vulvovaginal tissues, with loss of subcutaneous fat. There may be fusion of the labia minora and new urethral prominence [2] (Fig. 1).

Diagnosis

This is primarily a clinical diagnosis based on postmenopausal status and classic symptoms; however supporting evidence can be obtained by exam and the presence of parabasal cells on wet mount.

Treatment

First-line therapy for mild to moderate symptoms is nonhormonal. Vaginal moisturizers which are products intended to trap moisture in the vaginal tissue should be used at least twice weekly, and these have been shown to improve dryness and

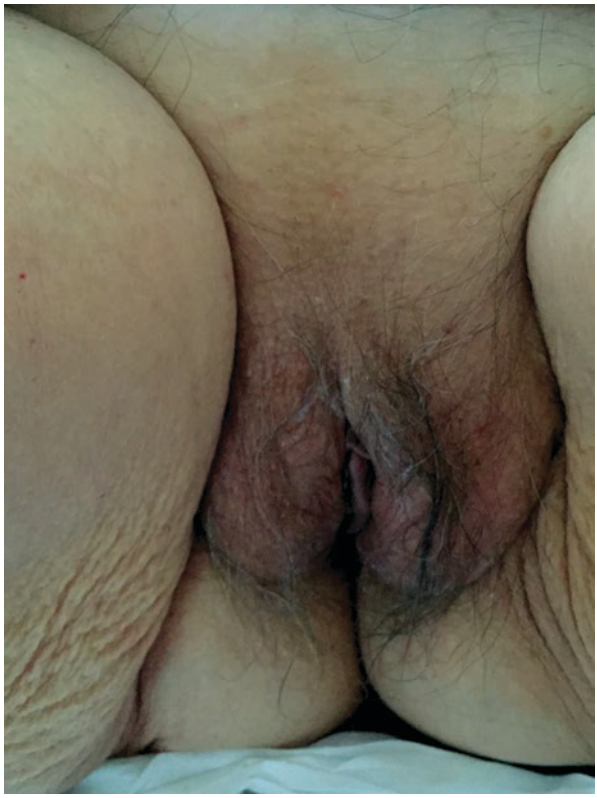

Fig. 1 Menopausal changes post treatment – A. Clouse

elasticity and to reduce itching, irritation, and dyspareunia [2]. Water- or silicone-based lubricants can be used on an as-needed basis before sexual activity.

If this approach is inadequate, the next step is hormonal therapy. If genitourinary complaints are the primary symptoms of concern, then low-dose topical estrogen are safe and effective. Options include estrogen creams, vaginal estrogen tablets, and estrogen-releasing vaginal rings; however the most common formulation is vaginal estrogen cream. Typically these are given daily for 2 weeks, followed by twice-weekly dosing as maintenance (rings are left in longer). Most women experience improvement within 2–3 weeks. This helps stimulate regrowth of the normal superficial epithelium of the vagina and urethra, with concomitant decrease in pH, return of lactobacilli, and increase in secretions. Urinary symptoms improve as well, with a decrease in recurrent UTIs and, in some cases, improvement in symptoms of overactive bladder [4].

There is minimal systemic absorption, and there are no recommendations to add progesterone to protect the endometrium [2, 4]. Risks of long-term therapy beyond a year are undefined, and there are no randomized controlled trials greater than this length of time [4]. There have been no significant differences found between various

products and formulations [4]; creams have the advantage of being applied directly to the vulva and urethral areas.

Systemic hormones are a reasonable approach for women with GSM who also experience problematic vasomotor symptoms. These can be delivered orally, transdermally, or via vaginal ring. Progesterone must be added for any woman with an intact uterus to prevent uterine hyperplasia. Note that there are vaginal rings formulated to deliver either local doses of estrogen or systemic doses of estrogen and as with any systemic estrogen, progesterone must be added for women with an intact uterus. The North American Menopause Society recommends starting hormonal therapy in women less than age 60 or within 10 years of menopause [5]. Within this time frame, the risk of heart disease does not seem to be increased [5]. There are known risks of venous thromboembolism (VTE) and breast cancer associated with hormonal therapy, and patients should be risk-stratified before beginning therapy; routine screening with mammograms is recommended. VTE risk can be decreased by using a transdermal delivery system thereby bypassing liver metabolism [4]. The lowest dose for the shortest amount of time should be used.

The selective estrogen receptor modulator (SERM) ospemifene has agonist activity in vaginal tissue and has been approved for the treatment of moderate to severe dyspareunia associated with menopause, although it has not been recommended as a first-line therapy [4].

Lichen Sclerosus

Epidemiology

Lichen sclerosus is an inflammatory condition affecting primarily the vulva and perianal regions in women, although it can also affect men and children. It is generally a concern of postmenopausal women with an average age of onset in the fifth or sixth decade [6, 7]; however a bimodal age distribution has been described with a second peak in girls averaging 5 years of age [8, 9]. It is estimated to occur in 0.1% of girls and 3% of postmenopausal women [9].

Pathogenesis

The exact cause of lichen sclerosus is unknown, although it is widely accepted to be an autoimmune phenomenon. The most common associated conditions are thyroid disorders, alopecia areata, and vitiligo; other conditions include pernicious anemia, diabetes, bullous pemphigoid, lupus, and psoriasis [9–14].

Antibodies to the basement membrane zone and to the extracellular matrix were found in greater prevalence in patients with lichen sclerosus than in controls;

however they have not been demonstrated to be causative [15, 16]. Other autoantibodies such as antinuclear antibodies (ANA) have also been found in increased prevalence in LS patients [13], and there is an increase in family members who have autoimmune disease [10, 13]. Furthermore, there is likely a genetic component related to LS [9, 17].

Lichen sclerosus can present at sites of previously injured skin in a Koebner phenomenon. Surgery, episiotomy, sexual trauma, and circumcision can all trigger the onset of lichen sclerosus at the affected site [7, 17]. This is especially common for extragenital sites.

Research into other possible etiologic agents has been extensive. Because of the bimodal age distribution, some have postulated that LS is caused by the hypoestrogenic state; however there has never been shown to be any association with pregnancy, hysterectomy, contraceptive use, or hormone replacement therapy. A decrease in androgen receptors in the vulva has been found in patients with LS; however topical testosterone has not been an effective treatment, nor has topical estrogen or progesterone [9].

Infectious causes have also been investigated, including human papillomavirus (HPV), *Borrelia burgdorferi*, hepatitis C, and Epstein-Barr virus; at this time no causative relationship has been found [7, 18–20].

Clinical Features

Distribution has been described as "figure of 8," "keyhole," or "hourglass." Affected areas include the labia minora most commonly, followed by the clitoris, perianal region, and perineum. Mucosal surfaces are usually spared. Extragenital lesions are found in up to 13% of women on almost any site [21].

The appearance of the skin is classically described as "cigarette paper," indicating a thin, porcelain-white crinkled and atrophic appearance. Initially there may be white papules or plaques that later coalesce to form large atrophic areas, sometimes with erosions, ecchymosis, edema, tearing, or fissuring. Hyperkeratotic plaques are sometimes present (Fig. 2).

With advanced disease there may be architectural changes caused by the progressive scarring process. This can include fusion or resorption of the labia minora, narrowing of the introitus or rarely the urethral meatus, phimosis of the clitoral hood, and tissue bridging. A painful pseudocyst can form if adhesions seal over the clitoris trapping keratinous debris [17].

The most common symptom is pruritus, worse at night and disrupting sleep. Other common symptoms include soreness, burning, and pruritus ani. If scarring has caused stenosis or if skin has thinned to the point of tearing or fissuring, there may be dyspareunia, dysuria, or pain with defecation. Sexual dysfunction is common, and women with LS are more likely to report dyspareunia and decreased

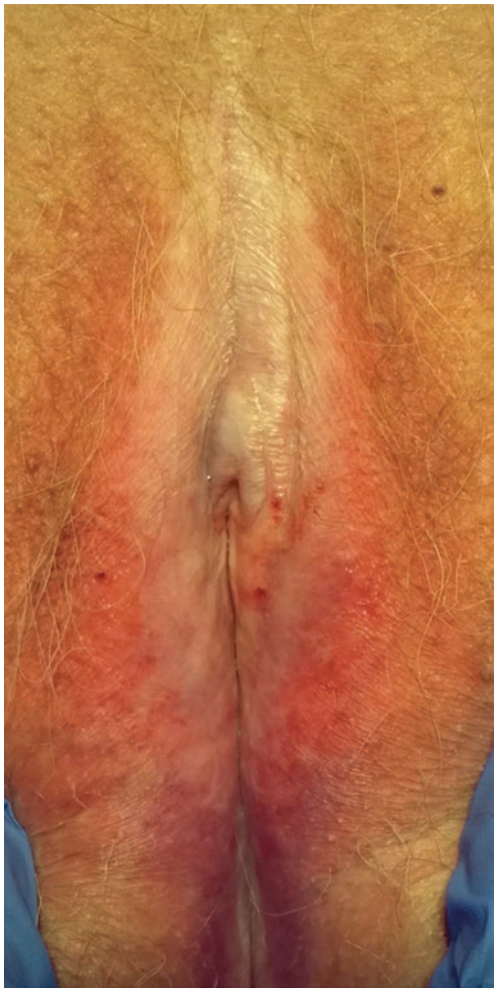

Fig. 2 Lichen sclerosus. (By Mikael Häggström – Own work, CC0, https://commons.wikimedia.org/w/index.php?curid=34245139)

arousal, lubrication, and orgasm [22, 23]. Neuropathic pain symptoms may persist even after treatment with apparent resolution of signs and symptoms.

Diagnosis

Debate exists over the need for biopsy to confirm diagnosis. The American College of Obstetricians and Gynecologists (ACOG) guidelines state that a biopsy is necessary to confirm diagnosis [6]; British dermatology guidelines and European Academy of Dermatology guidelines state the biopsy can be bypassed if the clinical features are typical [9, 17]. A survey of members of the International Society for the

Study of Vulvovaginal Disease (ISSVD) showed that only 35% of members always biopsy at the initial visit to establish the diagnosis; the remaining society members biopsy if the diagnosis is unclear [24].

Treatment

Goals of treatment include symptom improvement and resolution of at least some clinical signs. Hyperkeratosis, bruising, fissures, and erosions are more likely to improve than atrophy and scarring [17].

Potent and ultrapotent steroids remain the gold standard for treating lichen sclerosus. Clobetasol propionate 0.05% cream is the most commonly used ultrapotent steroid. For acute symptoms clobetasol is given in a variety of tapering regimens approximating once daily for 4 weeks, then every other day for 4 weeks, then twice weekly for 4 weeks. Once-daily dosing is adequate for ultrapotent steroids [17]. It is generally agreed that a 30 g tube of an ultrapotent steroid should last 3–6 months. Safety and efficacy of this regimen and of long-term use has been demonstrated. In one study of 327 patients treated in England with a similar regimen, 96% had symptomatic improvement, 66% became symptom-free, 23% had total resolution of clinical signs, and 68% showed partial resolution of clinical signs [8]. Maintenance therapy is administered either on an ongoing less frequent dosing schedule, such as twice weekly, or else on an as-needed basis.

Evidence is mounting for the use of mometasone furoate 0.1% which is a mid-potency steroid cream as an alternative to clobetasol. Two randomized controlled trials comparing clobetasol to mometasone for treatment of LS did not find significant differences in efficacy for acute symptoms [25, 26]. If clobetasol is used as induction therapy, mometasone has been found to be effective as maintenance therapy [9].

Topical calcineurin inhibitors including tacrolimus 1% and pimecrolimus 1% have been researched as an alternative to steroids. In particular, pimecrolimus has shown good efficacy in clinical trials [27–29]. These medications are often used as second-line treatment options for recalcitrant disease. Care should be taken in their use; the FDA has placed a black box warning on these agents stating that rare cases of malignancy have been reported, and they should only be used intermittently in the smallest doses possible and only as second-line agents [30, 31].

Other second-line agents that have been shown to be effective include local corticosteroid injections [9], UVA1 phototherapy [32], and topical retinoids [7]. Moisturizers have been shown to be helpful to maintain remission [33]. Very resistant cases may respond to systemic therapies like pulsed steroids, cyclosporine, methotrexate, and hydroxycarbamide, although these have not been well studied [17]. Topical lidocaine, tricyclic antidepressants, and gabapentin have all been effective for treating pain [18]. Surgery, which was once a common treatment for intractable itching, should be reserved for problems related to scarring, intraepithelial neoplasia, or cancer [9].

Risk of Malignancy

Lichen sclerosus is considered a premalignant condition and is one of the two main precursors of vulvar intraepithelial neoplasia (VIN), the other being the human papillomavirus (HPV). Theories on why this happens include chronic inflammation, failure of immune surveillance in an autoimmune environment, and cytogenetic factors [31]. Lifetime incidence of squamous cell carcinoma (SCC) in lichen sclerosus is estimated to be around 5%, with an average preceding period of disease of about 10 years [34]. On histologic exam, approximately 60% of vulvar squamous cell carcinomas are found to occur in a background of lichen sclerosus [17, 21, 31, 34]. There are reports of vulvar verrucous carcinoma associated with lichen sclerosus [35]. Other cancers have not been shown to occur in increased frequency.

Age greater than 60 and the presence of hyperplasia were identified as patient characteristics associated with developing SCC in one chart review; however clinical signs and disease duration did not seem to have a similar association [36].

At this time there is inadequate evidence to say if treating the signs and symptoms of the disease contributes to preventing malignant progression. One study with long-term follow-up did find that malignancy occurred only in the group of patients who admitted noncompliance with therapy [37].

Follow-Up

Patients should initially be seen by a specialist; however once stabilized ongoing surveillance can be done in the primary care office and can be annual in the well-controlled patient [6]. However, relapse rates are high; one study noted 84% at 4 years [38]. Based on guidelines for follow-up from the ISSVD, re-referral to a specialist should be made if the patient is requiring topical steroids more than three times per week for symptom control; if the patient has a finding of VIN or vulvar SCC on biopsy or has a history of either of these; if there is hyperkeratosis present; if the pathologist expresses concern but cannot make a definitive diagnosis on biopsy [34].

Patients should be educated about the risk of cancer and encouraged to do vulvar self-exams at home. For any findings of new growths or skin changes or persistent ulcerations, they should return to their PCP for evaluation. Areas of persistent hyperkeratosis or erosions, warty lesions, hyperpigmented areas, or treatment-resistant areas should be biopsied [7].

Lichen Planus

Epidemiology

Estimates of lichen planus (LP) affecting any site in the general population range from 0.5% to 2.3% [39]. There is a slight predominance in women affected. For the vulvar and vaginal variants of lichen planus (VVLP), exact prevalence is unknown.

Mean age of symptom onset is generally in the sixth or seventh decades [40–44], with an age range given from 20s to 90s [40, 41].

Pathogenesis

Lichen planus is generally accepted to be an autoimmune phenomenon; however the mechanisms are poorly understood. Like lichen sclerosus, there is an increased prevalence of other co-occurring autoimmune disorders (29% of cases vs 9% controls), with thyroid disease as the most prevalent, followed by alopecia areata and celiac disease [11]. There is an increase in autoantibodies found in the sera of affected women, mainly antithyroid and antinuclear [11]. Antibasement membrane zone antibodies were found in the sera of 61% of patients with erosive LP in one study, although this is not thought to be causative [11].

There have been documented associations between certain medications and incidence of LP. Nonsteroidal anti-inflammatory drugs and beta blockers were significantly more likely to be used by patients with LP in one study, while ACE inhibitors were found to have a statistically significant inverse relationship [41].

Clinical Features

Classic LP presents as a cutaneous rash in the form of violaceous polygonal papules and plaques primarily over the wrists and lower legs [44]. Wickham's striae, fine reticular white streaks, are pathognomonic. Oral LP presents with a variety of patterns, classically hyperkeratosis and Wickham's striae; however it may also be erosive, atrophic, papular, bullous, or plaque-like. Other affected body sites can include scalp leading to scarring alopecia, fingernails, esophagus leading to dysphagia, external auditory meatus leading to deafness, and lacrimal ducts.

Vulvar and vaginal LP presents with three distinct morphologies. The classic subtype is similar to cutaneous lesions, with violaceous papules, Wickham's striae, and post-inflammatory changes [45]. The hypertrophic subtype consists of white hyperkeratotic plaques. The erosive subtype is the most common and the appearance is commonly described as "scalded." It consists of symmetric well-demarcated erythema and erosions with a white lacy edge [43, 44]. Scarring with architectural changes is common, including loss of labia minora, burial of the clitoris, and if the vagina is affected, synechiae leading to stenosis of the introitus and vaginal walls (Fig. 3).

The vulvovaginal-gingival syndrome or plurimucosal lichen planus is a term used to describe LP that affects vulvar, vaginal, and oral mucosas. Estimates of the prevalence of vulvar/vaginal disease in those with oral disease range from 16% to 75% [39, 41, 46]. Because of the likelihood of co-occurrence at multiple sites and

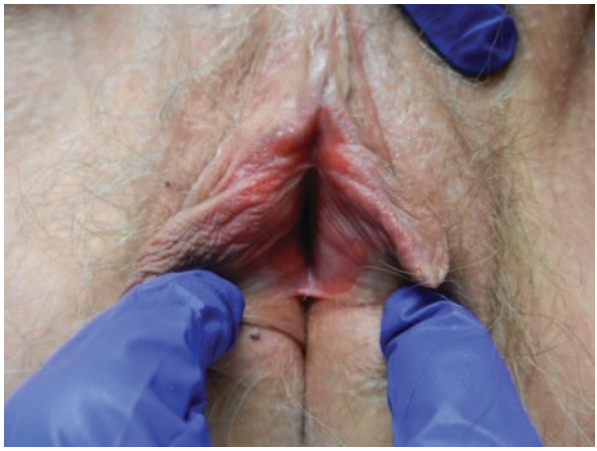

Fig. 3 Lichen planus. (Courtesy of Diane Elas, ARNP)

the possibility of asymptomatic clinical findings, it is recommended that a full body exam be done at the time of diagnosis.

Symptoms

The most common presenting symptoms are pruritus and vulvar irritation. In the erosive subtype, a seropurulent vaginal discharge is common. Symptoms related to scarring may include entry dyspareunia, apareunia, postcoital bleeding, dysuria, poor urinary stream, or difficulty obtaining cervical smear. A review of 114 women with VVLP found that 95% had some degree of scarring, ranging from mild to severe, present at the time of diagnosis [40]. At one vulva clinic, it was documented that 70.6% of 58 women with VVLP were abstinent at the time of diagnosis [44]; in another review of 95 women, 44 had abstained from vaginal intercourse for at least a year [43].

Diagnosis

A biopsy should be obtained to confirm diagnosis and to rule out vulvar intraepithelial neoplasia (VIN) or malignancy. Histologically there may be only inconclusive inflammation and erosion, or there may be the classic findings of a hyperkeratotic epidermis, sawtooth rete ridges, a lymphocytic infiltrate, and degeneration of the

basement membrane with cytoid bodies (necrotic keratinocytes) [44, 45, 47]. Vaginal discharge will likely have a high pH, and wet mount typically shows many white blood cells, increased parabasal (immature squamous) cells and decreased normal keratinocytes, and absent lactobacilli [47].

Treatment

A Cochrane review in 2012 found no randomized controlled trials on treatment of vulvar LP; there is a need for research in this area [48]. The standard of care for first-line treatment is potent topical corticosteroids, typically clobetasol, dosed in a tapering regimen over 3 months. Many women experience improvement with topical steroids, although for many the improvement is incomplete and they require multimodal treatments. Nonresponder estimates for steroids range from 18% to 35% [40, 44–46].

Second-line treatment choices vary. Topical calcineurin inhibitors have shown efficacy in treating recalcitrant cases: in one review of 16 nonresponders to topical steroids, 15 improved with tacrolimus [49]. Topical pimecrolimus may be better tolerated with less burning on application and has shown similar efficacy [50].

Vaginal hydrocortisone suppositories twice daily are effective for vaginal symptoms [51]. Intralesional injections of triamcinolone acetonide can be used as second line for resistant or hyperkeratotic plaques. Systemic treatments including pulsed oral steroids, methotrexate, hydroxychloroquine, and dapsone have all been cited as preferred second-line agents at varying sites, but benefits are inconsistent [42, 46].

Scarring does not reverse with medical treatments, and if severe, requires surgical intervention for lysis of vaginal adhesions or perineotomy for vulvar fusions. Lifelong dilator therapy and intravaginal steroid use are necessary after surgery [52].

Prognosis

There are reports of squamous cell carcinoma (SCC) associated with LP. A systematic review combining four case series with long-term follow-up found five cases of vulvar SCC in 366 combined patients [53]. In a review of 114 women with VVLP, seven developed VIN and three developed SCC [40]. Reported risk of malignant progression is 2–3% [46]. Because of this, regular follow-up on a long-term basis with biopsy of any unusual lesions is prudent.

Overall, while cutaneous LP typically resolves on its own after 2–4 years, mucosal LP is generally a chronic relapsing-remitting disorder.

Lichen Simplex Chronicus

Epidemiology

Lichen simplex chronicus (LSC), also known as neurodermatitis, is a chronic pruritic dermatitis that can affect both men and women of all ages; adult women are affected slightly more frequently than adult men [54]. As with many of the other vulvar disorders, the exact prevalence is unknown. Within a vulva specialty clinic, estimates range from 10% to 35% of patients that are affected by vulvar LSC [54].

Pathophysiology

LSC has been referred to as the "itch which rashes." Any number of causes may lead the patient to start to itch, and with repetitive itching the characteristic skin changes of LSC develop, including hyperplasia and inflammation. These skin changes perpetuate the itching, known as the "itch-scratch-itch" cycle.

The initial itching may be prompted by a variety of insults. Triggers may include environmental factors such as heat, clothing, menstrual products, and personal hygiene products. Other patients may have an underlying skin condition such as lichen sclerosus, psoriasis, eczema, or allergic or irritant dermatitis that initiates the itch-scratch-itch cycle. There is an increased prevalence of personal or family history of atopy in patients with LSC [54]. There is debate about the role of stress and underlying anxiety disorders [54].

Symptoms

This intense and intractable itch is truly the most characteristic symptom of LSC. Affected persons may describe a sense of pleasure and relief associated with scratching, and they may scratch until they damage the skin, replacing the itching with a preferable pain sensation. The scratching may occur subconsciously, especially at night. Factors such as stress, heat, sweat, and friction from clothing may intensify the itching [55].

Clinical Features

LSC can affect any part of the body. Vulvar LSC primarily affects the labia majora, although the labia minora, vestibule, mons pubis, thighs, and perianal region may also be affected [54, 56].

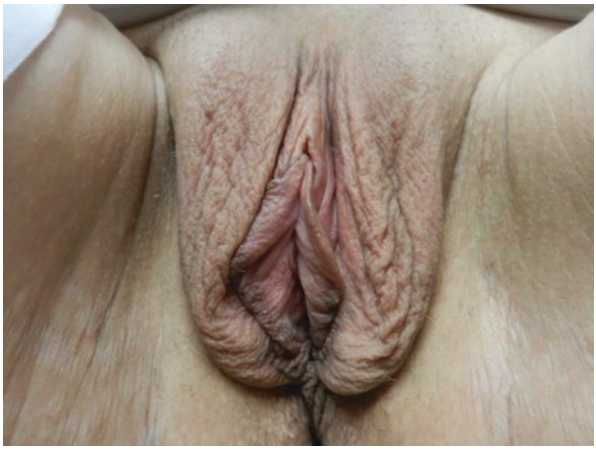

Fig. 4 Lichen simplex chronicus. (Courtesy of Diane Elas, ARNP)

The rash can be uni- or bilateral. Affected skin will appear thickened or "lichenified," and this may be palpable on exam. Skin discoloration can range from erythema to white or brown, with accentuated skin markings and linear or angular excoriations [55]. Healed areas may be hypopigmented, particularly in patients with darker skin. Papules are sometimes seen and fissures can be present as the thickened skin is less flexible [54] (Fig. 4).

Diagnosis

This is primarily a clinical diagnosis based on classic exam findings and history. A biopsy can help to confirm but is not necessary. Histologic findings include an irregular thickening of the epidermis with hyperkeratosis and an inflammatory infiltrate [57]. A biopsy may be helpful to rule out underlying skin disorders; however it may be obscured by inflammatory changes; if negative it can be repeated after treatment.

Treatment

Treatment goals are multiple, including repairing the skin barrier, reducing inflammation, and interrupting the itch-scratch-itch cycle [54]. Initial repair of the skin can be accomplished by avoiding further irritants and not scratching. Patients should avoid sprays, wipes, douches, and any other over-the-counter treatments, and wash only with hands and water – no scrubbing [57]. Non-allergenic emollients and loose clothing can help soothe irritated skin, and sitz baths, cool compresses, and handheld shower heads can be used to relieve itching [57]. Antihistamines and sleep promoters such as tricyclic antidepressant medications can help with nighttime itching.

High potency topical steroids such as clobetasol remain the first-line treatment for reducing inflammation and decreasing lichenification. These can be weaned to less potent maintenance regimens as able. Topical calcineurin inhibitors have been shown to be effective; however these remain a second-line therapy [55, 58].

Treatment can lead to remission, but this is a chronic condition that may relapse. There is no known association with malignancy of LSC; however underlying conditions should be identified and treated, as they may require ongoing surveillance.

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Dermatoses in Pregnancy

Renell S. Dupree and Stephen Smith

Pregnancy dermatoses describe a set of extremely pruritic dermatologic disorders that uniquely present in the gestational period. They are pruritic urticarial papules and plaques of pregnancy (PUPPP), pemphigoid gestationis (PG), atopic eruption of pregnancy (AEP), and intrahepatic cholestasis of pregnancy (ICP). While the most common of these, AEP and PUPPP, are benign, self-limiting diseases that have no implications for the fetus, PG and ICP both pose a risk to the fetus and are associated with adverse outcomes. In the early stages of PG, it can be indistinguishable from PUPPP which can delay appropriate treatment and monitoring. In the case of ICP, women with this disorder are also at increased risk of developing other pregnancy-related disorders, namely, gestational diabetes and pre-eclampsia, both of which also pose adverse risk to the fetus. Having a good understanding of the presentation, clinical course, and treatment of these dermatologic conditions is key for appropriate diagnosis and timely treatment—in order to prevent adverse outcomes for moms and babies and, in the case of benign conditions, improve the quality of the pregnancy experience.

Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP), also known as polymorphic eruption of pregnancy (PEP), is one of the most common dermatologic conditions in pregnancy. It is characterized by erythematous papules that initially occupy the abdominal striae, with periumbilical sparing, and later coalesce to urticarial plaques that are seen mostly on the abdomen, buttock, and lower

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extremities (Fig. 1). It was first described in 1979 based on a series of case studies of women presenting with a similar pruritic rash in the third trimester [1].

The incidence is between 1:120 and 1:200 [2]. PUPPP is more prevalent in Caucasian women, primigravidas, multiple gestations, and excessive weight gain [3]. It is usually seen in the third trimester; however, initial presentation can occur in postpartum period [4]. Earlier onset has been described in multiple gestations and multigravidas. Multigravidas are also associated with longer duration of disease [3]. This is a benign condition with no documented effects on the fetus.

The pathogenesis of PUPPP is unknown. Theories suggest that it could be related to the destruction of connective tissue and subsequent activation of the immune response secondary to abdominal distention or that it may represent an immune response to circulating fetal antigens [5, 6].

As with all pregnancy dermatoses, pruritus is the most common patient complaint. Erythematous papules and urticarial plaques are the most common presentations of PUPPP (Figs. 1 and 2). The erythematous papules frequently have a halo of hypopigmentation around them [1]. PUPPP can progress to include vesicles, targetoid lesions, erythema, and eczematous lesions [3], making the distinction from the pre-bullous state of pemphigoid gestationis difficult. However, PUPPP never presents with bullae [4]. Some cases, especially those with prolonged duration of disease, have seen more disseminated involvement to include the arms, palms, soles, face, etc. [1, 3].

PUPPP is diagnosed clinically based on classic presentation and clinical course. Laboratory data and biopsy specimens are only indicated with unusual presentations or failure to improve with treatment. In these cases, laboratory data can help exclude intrahepatic cholestasis of pregnancy, and direct immunofluorescence of biopsy specimens will help to rule out pemphigoid gestationis [4, 7–9].

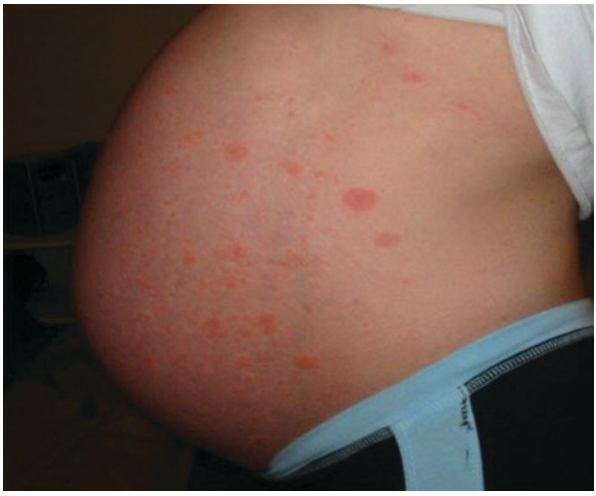

Fig. 1 PUPPP, 36 weeks' gestation (Wikimedia commons-Heykerrian)

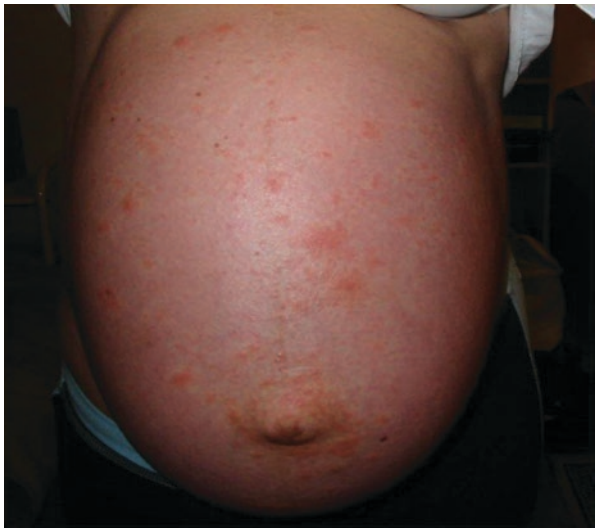

Fig. 2 PUPPP of abdomen, 36 weeks' gestation (Wikimedia Commons-Heykerrian)

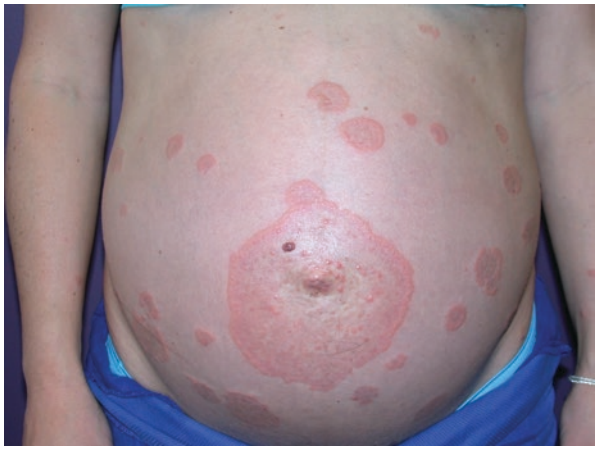

Fig. 3 Pemphigoid gestationis—DERMNET NZ

Topical corticosteroids are the treatment of choice for PUPPP. Antihistamines are often prescribed as adjunctive therapy as well. The majority of cases have good response. In rare, severe cases, treatment with oral corticosteroids is indicated. PUPPP usually resolves within 4–6 weeks of delivery. It usually does not recur with subsequent pregnancies. Both maternal and fetal outcomes are favorable.

Pemphigoid Gestationis (PG), formerly known as herpes gestationis, is the only autoimmune disorder unique to pregnancy. It is characterized by erythematous papules and urticarial plaques that can form into more targetoid lesions, and the hallmark of this disease is eventual bullous formation (Fig. 3). PG presents very similar to PUPPPS and, in forms of the disease that do not include bullous formation, it is very difficult to distinguish the two.

PG is seen in 1/20,000–1/50,000 pregnancies [7, 8, 10]. Rarely, PG is associated with trophoblastic tumors, hydatidiform moles, or choriocarcinoma. It usually presents in the second or third trimester, although it can present earlier in subsequent pregnancies. There is a strong association between PG and the presence of the maternal alleles HLA D3 and D4 (61–80% and 52%, respectively.) [7]. Graves' disease is seen in 10–11% of PG patients [11].

In PG, autoantibodies develop against the basement membrane protein collagen XVII (BP180). This protein is present in the basement membrane zone of the skin as well as the placenta and umbilical cord [7, 9].

Formation of antibody-antigen complexes causes the activation of the complement system and subsequent recruitment of eosinophils leading to the destruction of the dermal-epidermal junction resulting in the skin manifestations present in PG. This is thought to occur in the setting of abnormal expression of MHC II molecules on the surface of the placenta which leads to the development of these autoantibodies [7, 9]. Of note, autoantibody levels are thought to be affected by changes in estrogen and progesterone levels such that when estrogen levels are high and/or progesterone levels are low, there is more abundance of autoantibodies and subsequent worsening clinical manifestations [7, 9].

Pruritus is usually the presenting symptom. This is followed by or in conjunction with the formation of a rash that presents initially quite similar to PUPPP with erythematous papules and urticarial plaques. Unlike PUPPP, the umbilicus is usually the site of initial involvement. The rash then spreads to include the rest of the abdomen, trunk, arms, and legs (primarily thighs). PG usually does not affect the face or mucosal membranes, but some cases have been described [8]. Targetoid lesions can form as well (Fig. 3). Ultimately the disease will progress to bullous formation which then can burst causing hyperpigmentation of the skin and erosions. PG is diagnosed using direct immunofluorescence. It will show a linear distribution of C3 along the basement membrane zone. ELISA assay using serum to detect the anti-BP180 autoantibody can be helpful both in diagnosis and monitoring, as the levels correlate to severity of disease and disease resolution with treatment [7, 9].

Corticosteroid therapy is the treatment of choice for PG. Mild cases can be treated with topical corticosteroids; however most cases require oral steroids. Prednisolone is preferred over prednisone as it is safer in pregnancy [11]. Adjuvant therapy with antihistamines and warm compresses aid in symptom relief. In severe and prolonged cases, immunologic agents, anti-inflammatory antibiotics, IVIG, plasmapheresis, and luteinizing hormone-releasing hormone have been used with varying effectiveness [7–9, 11].

PG tends to occur in the second or third trimester. With treatment, it usually improves toward the end of pregnancy. However, in 75% of pregnancies, it flares again at the time of delivery, linked to a drop in progesterone levels [9]. Symptoms usually completely resolve within 6 months postpartum. Rare cases of prolonged PG have been cited [12, 13]. It recurs in 90% of subsequent pregnancies and tends to have an earlier onset and more severe disease course [7, 9, 14]. Reoccurrences have been seen in the premenstrual period and with oral contraceptive (OCP) use [7, 9].

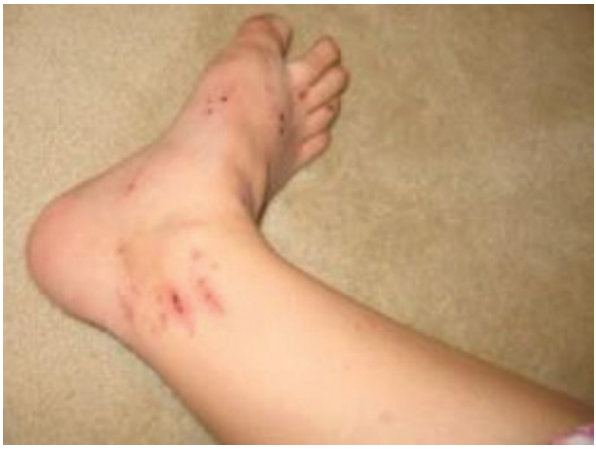

Fig. 4 Multiple excoriations secondary to intense pruritus associated with ICP (Wikimedia commons)

Pregnancies affected by PG are at higher risk for low birthweight infants and prematurity. This is thought to result from the destruction of the placenta from circulating autoantibodies [9]. In 10% of cases, infants show some self-limiting skin manifestations owing to the transfer of IgG antibodies [7]; however, there are no associated effects on infant morbidity or mortality.

Intrahepatic Cholestasis of Pregnancy (IHCP) is unique in that it is the only pregnancy dermatosis that presents without a rash. IHCP presents with severe pruritus and elevated serum bile acids. When a rash does form, it can include excoriations and prurigo nodules that form in response to severe itching (Fig. 4). It is the most common hepatic disorder of pregnancy. IHCP is seen in 0.3–5.6% of pregnancies [15]. Some studies have shown it to be more prevalent in the Latino and Asian ethnicities [16, 17]. Other risk factors include advanced maternal age, history of cholestasis with OCP use, gallbladder disease, IHCP in a previous pregnancy, and family history of IHCP [15, 18]. IHCP usually presents in the third trimester of pregnancy. Earlier manifestation of disease is associated with worse outcomes [19].

The pathogenesis of IHCP is not completely understood. The current thinking is that it is related to cholestasis induced by elevated estrogens in genetically predisposed women. In terms of its effects on the fetus, it is thought that bile acids, which freely cross the placental membrane, may exert effects on the cardiac myocytes, cause vasoconstriction of cord vessels, and exert effects on cells of both the gastrointestinal and pulmonary systems of the fetus, leading to adverse fetal outcomes associated with this disease. Recurrence of IHCP is high in subsequent pregnancies [18, 20]. Interestingly, although IHCP tends to recur in subsequent pregnancies, it is actually associated with decreased fetal complications in subsequent episodes [16].

Pruritus, especially of the palms and soles, is usually the presenting complaint in IHCP. The diagnosis is made when serum bile acids (bilirubin) are shown to be elevated, usually >10 g/dl. Other markers including AST, ALT, alkaline phosphatase, and GGT may also be elevated [20–22], but not always. Jaundice is not a common symptom and is associated with <25% of cases, so if present, further workup

for alternative etiologies is recommended [15]. It is also recommended that an ultrasound be performed in these patients to rule out cholelithiasis [15].

IHCP increases the likelihood of other pregnancy complications as well as adverse neonatal outcomes. In prolonged cases, absorption of fat-soluble vitamins and resulting coagulopathies (secondary to vitamin K deficiency) can increase the risk for intrapartum and postpartum hemorrhage [21]. IHCP has been shown to be associated with preterm delivery, meconium stained amniotic fluid, fetal distress, and perinatal death. These adverse fetal outcomes correlate with increasing bile acid levels, with most seen at bile acid levels >40 and perinatal death being most commonly associated with levels >100 [21]. It is also associated with more large for gestational age babies and babies that overall fit into larger growth percentiles [23]. Women diagnosed with IHCP are also at increased risk for development of gestational diabetes mellitus [17, 23, 24], pre-eclampsia, and an abnormal lipid profile [23]. Interestingly, diagnosis of GDM and pre-eclampsia was made in women who had previously screened negative prior to the development of IHCP, highlighting the importance of reevaluation of these disorders once IHCP is diagnosed [23, 24].

The treatment of choice for IHCP is ursodeoxycholic acid (UDCA) (10–15 mg/kg [15]). UDCA's effectiveness at reducing pruritus and serum bile acid levels is well documented. It may also be beneficial at reducing fetal outcomes [25], although this is less clear in the literature. While abnormalities related to the development of GDM improve with UDCA treatment, it does not appear to improve abnormal lipid levels or cause resolution of pre-eclampsia. Delivery is recommended at 37 weeks as this is associated with better fetal outcomes. IHCP resolves with delivery. Like PG, rare recurrences have been reported with the use of OCPs.

Atopic Eruption of Pregnancy (AEP) refers to three conditions: atopic dermatitis (AD), prurigo of pregnancy (PP), and pruritic folliculitis of pregnancy (PFP). AEP is the most common pregnancy dermatosis with AD being the most common presentation.

The incidence of AEP that varies in the literature is found to be from 19.7% to 50% of all pregnancy dermatoses [26]. AEP usually occurs before the third trimester, and most patients are thought to have an atopic background which includes either personal or family history of atopic disease [4]. However, for 80% of pregnant patients, the eruption in pregnancy is their initial manifestation of atopic disease [4].

Although not fully elucidated, AEP is thought to occur secondary to the immunologic switch that occurs in pregnancy resulting in a dominant humoral, Th2 cytokine producing response as it is a Th2 mediated disease [4, 26].

AEP presents in two forms: the eczematous type (E-type) refers to the presentation of an eczematous rash in the flexor surface of the arms and legs as well as the face, neck, and chest [27]. The papular type (P-type) refers to pruritic erythematous papules on the trunk and limbs and prurigo nodules located mostly on the arms and legs [27] (Fig. 5). AEP is a clinical diagnosis. Labs and biopsies are only indicated to differentiate from other pregnancy dermatoses and/or acute and chronic dermatitides. IgE serum levels have been shown to be elevated in AEP [4]. Treatment is based on severity and usually involves emollients, anti-itch creams, topical steroids,

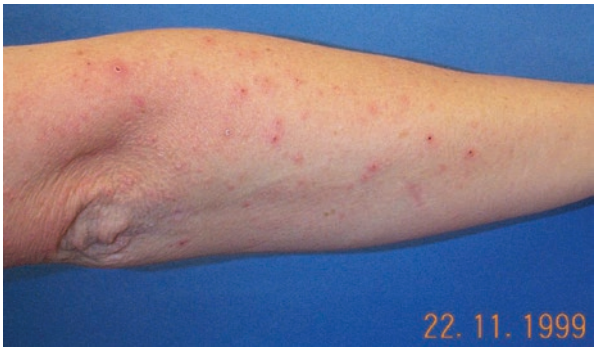

Fig. 5 Atopic eruption of pregnancy—DERMNET NZ

and oral antihistamines. Severe cases may require a short course of oral steroid therapy. Narrowband UVB phototherapy, with folate supplementation, can be used as a second-line treatment or first-line treatment in the first trimester [26]. Bacterial superinfections can occur and should be treated with appropriate antibiotics.

AEP is a benign, self-limiting condition that usually resolves within 3 months of delivery. It can recur in subsequent pregnancies. There is no associated harm to the mother or fetus. Of note, there is controversy in the literature over the grouping together of these disorders as AEP. These critiques point out flaws in the study design and interpretation that coined the term AEP as well as question the overlap of clinical presentation, with PFP in particular [26, 28]. More studies are needed to appropriately address these concerns and further characterize these disorders.

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The Diagnosis and Treatment of Common Wounds Encountered in Primary Care

Tracey L. Roesing and Jonathan Andrews

Patients often present to their primary care providers when they experience an open wound. It is estimated that there are 6.5 million patients suffering from chronic wounds in the United States, resulting in an estimated 25 billion dollars in annual medical expenses [1]. Primary care providers play a direct role in the initial and ongoing treatments for a broad range of wound types. These include acute trauma wounds, diabetes-associated wounds, and arterial or venous ulcers, to name a few. Through coordinated efforts and diligent follow-up to prevent and treat the aforementioned wound types, good long-term clinical outcomes are possible. In this chapter, the authors review the basic principles of wound healing and utilize current evidence to offer some clinical strategies involved in the treatment of the most commonly encountered wounds in the primary care setting.

The Four Stages of Wound Healing

Wound healing has classically been divided into four overlapping stages: hemostasis, inflammation, wound proliferation, and tissue remodeling. Within each stage, specific events occur that lead to the formation of the initial granulation tissue and the transformation of the wound bed into fully matured scar tissue. This entire process begins at the outset of the initial trauma.

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Immediately following tissue injury, vasoconstriction occurs in response to thromboxane release, which aids in limiting blood loss. During tissue injury, platelets are exposed to interstitial connective tissues and subendothelial elements (microfibrils, laminins, and collagens), leading to activation and aggregation at sites of vessel injury, along with fibrinogen and thrombin [2]. Platelet plug formation and fibrin deposition occur at the site of vessel injury and primarily help to reduce blood loss [3]. Additionally, the resulting fibrin-fibronectin meshwork that forms acts as a temporary scaffold in the early wound bed, providing inflammatory cells, fibroblasts, and myofibroblasts an early road map for wound repair [2]. Shortly after hemostasis is achieved, histamine release leads to vasodilation which increases the porosity of surrounding blood vessels, allowing easier access to the developing wound bed by leukocytes [4].

The inflammatory stage is heralded by the increased influx of polymorphonuclear leukocytes (PMNs) to the site of injury by way of chemokines and other factors (fibronectin, platelet-derived growth factor) [5]. PMNs remain active in the wound bed during the inflammatory phase for 1–2 days and release granules containing free radicals which help sterilize the surrounding area and proteases which degrade damaged tissues. Following the initial influx of PMNs to the site of injury, monocytes migrate to the wound bed and differentiate into mature macrophages, allowing them to phagocytose pathogens and damaged tissues [6, 7]. Additionally, stimulated by local tissue hypoxia, macrophages release pro-angiogenic factors enabling granulation tissue development and promoting the next phase of wound healing: proliferation.

Approximately 2–3 days following the initial tissue insult, the inflammatory phase of wound healing begins to subside with the decreased presence of many of the PMNs and macrophages that acted to sterilize and prepare the developing wound bed [8]. At this point during wound development, growth factors such as PDGF, TGF-β, and fibronectin attract fibroblasts to the site of injury and promote granulation of the wound bed. Upon their arrival to the site of injury, the fibroblasts secrete a material known as ground substance. Ground substance is a gel-like material which serves as a the extracellular matirix to which inflammatory cells, myofibroblasts and endothelial cells can adhere. Ground substance also provides lubrication for collagen fibers and serves to potentiate the formation of granulation tissue [3]. During the proliferative phase of wound healing, new blood vessel formation and epithelialization occur, permitting closure of the wound. Myofibroblast contraction accelerates this wound closure process and can continue 2–3 weeks following initial injury [9].

After proliferation and wound closure have occurred, scar formation and tissue remodeling take place and can last weeks to months after the original injury. During remodeling, durable type 1 collagen replaces the type 3 collagen meshwork initially secreted by fibroblasts [10]. It is during this longest phase of wound healing that the resulting scar develops its tensile strength with type 1 collagen deposition, approaching 80% of non-wounded tissue [11]. During this protracted phase of wound healing, pathologic scar formation, such as in the formation of wound contractures, hypertrophism, or keloid formation, can occur, often due to persistent inflammation and the pathologic upregulation of specific growth factors and regulators [8, 12].

Acute Trauma Wounds

Acute trauma wounds are very frequently encountered in the primary care and urgent care settings, making understanding and management of these types of wound imperative for the primary care physician. Two of the most commonly encountered acute wounds include burns (most commonly chemical or temperature related) and lacerations.

Burns

Burns can occur following exposure to chemical agents, extremes in temperature (hot or cold), electricity, friction, or radiation. The most common scenario involving burn injury is from hot liquids or from an open flame during cooking, with smoking and alcoholism acting as risk factors. The presence of burn injuries can also be associated with domestic violence or self-harm, and so clinicians are urged to obtain accurate history and physical examination during initial evaluation.

Burn injuries are classified according to the depth of injury. This ranges from first degree, being the most superficial, to fourth degree, which denotes injury extending to the underlying fat, muscle, and bone. Second-degree burns are divided into two groups, superficial partial thickness and deep partial thickness, which are determined by whether the extent of the burn is limited to the papillary dermis (superficial second degree) or extends beyond the reticular dermis (deep second degree). Third-degree burns extend through the entire dermis to, but not involving, the subcutaneous fat [13, 14].

Symptoms associated with burns include pain at the site of injury, erythema, edema, blistering, and in the case of severe fourth-degree burns, painless blanching [13]. Prognosis varies according to the type and extent of injury. Most first-degree to superficial second-degree burns heal relatively well with conservative measures (e.g., irrigation, cooling of the area, cleaning with soap and water, and dressings with or without topical antibiotics). Deep second-, third-, and fourth-degree burns require close observation as patients are at increased risk of fluid loss and infection [14].

In addition to the depth of injury, the percentage of total body surface area (TBSA) affected is calculated via the Lund-Browder method and categorized as either minor (<10% TBSA adults), moderate (10–20% adults), or severe (>20% adults) and is used to direct appropriate therapy [15]. For most moderate and severe burns, patients should be monitored in dedicated burn centers when possible, as these patients are at increased risk of insensible fluid loss and high risk of infection.

In severe burn injuries, post-injury complications can develop and pose challenging scenarios for patients and clinicians alike. Fibrosis and wound contractures represent the most frequent encountered post-burn scenario and are characterized by

excessive post-burn collagen production. Contraction of the wound site can lead to anatomic deformity and difficulty in performing acts of daily living for many patients [16]. Other post-burn complications, such as heterotopic ossification, can occur in specific patient populations; however current treatment modalities are limited [17].

Lacerations

Lacerations are frequently encountered in the outpatient setting. Lacerations are defined as irregular tear-like lesions typically caused by forms of blunt trauma. They can occur as isolated minor injuries or accompany larger total body injuries. During the initial assessment of the patient, it is imperative to assess the patient's cardiorespiratory status by evaluating their airway, breathing, and circulation (the ABCs), as further diagnostic workup and intense care may be needed in more significant injuries. For simple lacerations, standard wound care measures should be undertaken to minimize the risk of infection and promote early wound closure and healing. These include cleaning and irrigating the wound with sterile water and soap followed by closure with a variety of agents (sutures, adhesives, cyanoacrylate glue, staples, etc.). For patients who present >24–48 hours after the initial injury or if the area of involvement is too large to approximate the edges of the wound, healing by secondary intention without using additional closure agents (i.e., sutures) provides the best clinical outcome. The use of topical antibiotic ointments in the setting of simple, uncomplicated lacerations has not demonstrated benefit in terms of infection rate reduction, and is therefore not a standard treatment recomendation [18].

Diabetic Foot Wounds

Lower extremity wounds are a common cause for increased morbidity in diabetic patients, with an estimated increased risk of 25% in both type 1 and 2 diabetic patients compared to nondiabetic patients [19]. Needless to say, adequate preventative measures and outpatient follow-up can help reduce the risk of development of these wounds and their complications, decreasing patient morbidity and health system financial burden.

Prevention of wound development through proper lifestyle and foot hygiene adjustments has shown to have a positive benefit for patients and reduce ulcer development. This includes smoking cessation, not walking barefoot, daily foot inspections and washing with lukewarm water, and maintaining neatly trimmed toenails that conform to the shape of the toe. Custom shoes for patients with misshaped feet or those with previous ulcers may also help reduce the incidence of new ulcers [20, 21].

The development of foot ulcers in diabetic patients occurs most often in the setting of peripheral neuropathy. Unable to accurately sense and respond to pain and pressure, patients suffer repeated trauma to the skin and microcirculation of the foot, leading to ulcer development. Chronic neuropathy can lead to the formation of claw toes as a result of unopposed extension from the larger muscles of the lower leg against the waning ability of affected smaller intrinsic muscle groups of the foot. This leads to increased pressure exerted on the metatarsal head which, over time, predisposes the area to ulcer formation and is a common site of occurrence [22]. Other later complications of peripheral neuropathy in diabetics include diabetic neuropathic arthropathy, also called Charcot arthropathy. Charcot arthropathy is characterized by collapse of the arch of the midfoot and periarticular joint dislocation, leading to swelling, erythema, and anatomic deformity. Patients who develop diabetic neuropathic arthropathy are at significantly elevated risk of ulceration and its many associated complications (osteomyelitis, systemic infection) [23].

Stratifying diabetic foot wounds was first described by Wagner and relied heavily upon clinical appearance and evaluation of the ulcer; however it did not take into account vascular status of the patient's foot [24]. An updated model for classifying diabetic foot ulcers was introduced first at The University of Texas and included grading (0–3 based on wound depth) and staging (infected, non-infected, ischemic, ischemic and infected) of the wound [25]. The UT system has proven to be of significant benefit for accurate wound assessment and has inspired the development of additional classification schemes (WIfI, PEDIS) [26–28].

Treatment for diabetic foot ulcers begins with grading and staging of the wound, using the widely accepted UT classification scheme [26]. General care principles with regard to treatment include assessing the patients' overall clinical status, evaluating the presence of infection, and addressing poor glycemic control, arterial insufficiency, and bony deformities. Superficial non-infected ulcers (grade 0, stage A) can typically be debrided in the outpatient setting under local anesthesia. For deeper grade 2–4 ulcers, surgical debridement in the operating room is recommended, especially in the setting of infection and/or ischemia (stages B, C, D).

Dressing diabetic foot ulcers serves an important purpose in promoting healing and preventing infection. A variety of agents are available for use depending on the clinical status of the wound bed and include hydrogel, absorbent, and/or antimicrobial dressings and wound packing materials, such as sterile ribbons, for deep ulcers. Additionally, many adjuvant topical therapies exist that promote cellular regeneration and angiogenesis. Clinicians are advised to consider these adjuvants in patients at risk of infection and difficult-to-heal wounds. In cases of difficult-to-heal ulcers, hyperbaric oxygen therapy has been employed with varying levels of success [29, 30].

Following dressing of the wound, it is best to employ pressure offloading techniques for areas repeatedly exposed to trauma and/or frequent pressure. These techniques include the use of total contact casts, cast walkers, and custom shoes. Total contact casts are fiberglass or plaster shells that encase the entire foot, allowing for even distribution of pressure across the sole of the foot. This provides excellent healing for ulcers in the forefront of the foot and is the first-line therapy for uncomplicated, nonischemic, non-infected plantar ulcers [31]. Conversely, there are

disadvantages to using the total contact cast including the inability to inspect the affected foot, patient inconvenience for performing daily acts of living (bathing, etc.), and the possibility of additional wound development from improperly placed cast [32]. Cast walkers are similar in design to total contact casts; however they differ in their ability to be removed by patients themselves. Improvements in pressure offloading can be achieved using cast walkers compared to typical shoes; however the advantage over total contact cast remains to be determined. Disadvantages of cast walkers primarily include poor patient compliance, as the device can be removed unlike total contact casts. Following resolution of the wound, it is important for patients to use customized shoes with orthotic inserts to help prevent recurrence of ulcers. The use of prescriptive shoes has been shown to decrease the risk of re-ulceration of plantar-based ulcers and is generally recommended as an ongoing pressure offloading technique for patients who have had previous ulcers [33].

Venous Leg Ulcers

Epidemiology

A wound located on the lower extremity may result from one or a combination of several factors. Nearly 70% of all lower extremity ulcers are of venous origin. It has been estimated that, at any given time, 1% of the US population has a venous leg ulcer (VLU) [34]. Thirty to seventy percent of VLUs remain open and unhealed at 6 months, and up to 20% of VLUs remain unhealed for greater than a year. Risk factors for venous ulceration include obesity, advanced age, history of local injury, and history of deep venous thrombosis or phlebitis. Self-reported quality of life (QOL) scores are greatly diminished in the venous ulcer patient. In fact, studies suggest that rates of depression and low self-esteem correlate directly with the length of time a VLU remains unhealed [35]. These statistics add to the importance of recognizing and treating the patient with lower extremity venous disease as early as possible.

Diagnostic Signs and Symptoms

Leg edema and skin discoloration can be early signs of venous disease, often occurring even prior to ulcer formation (Fig. Fig. 1). Edema is usually a result of venous valve incompetence or inefficiency of the calf muscle pump mechanism, and the skin discoloration a result of capillary rupture and hemosiderin deposition over time.

Most venous ulcers are located above or near the medial malleolus, in the classic “gaiter” distribution. Venous ulcers usually have a shallow, moist wound bed with an irregularly contoured border (Fig. Fig. 2). Varying degrees of fibrin and slough deposition can be seen, and the venous ulcer patient will report varying degrees of mild to moderate pain [36].

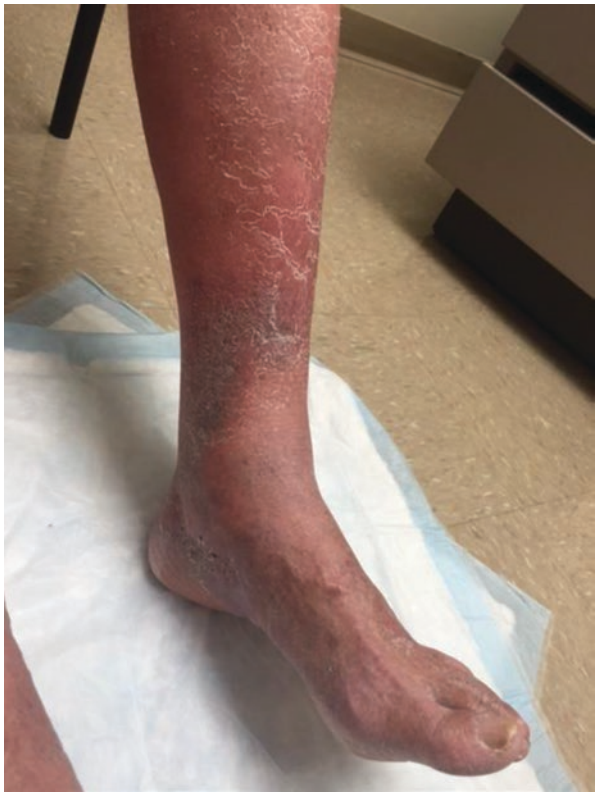

Fig. 1 Venous insufficiency, with evidence of edema, small varicosities, a healed area of former ulceration over the medial malleolar region, and resultant hemosiderin skin staining

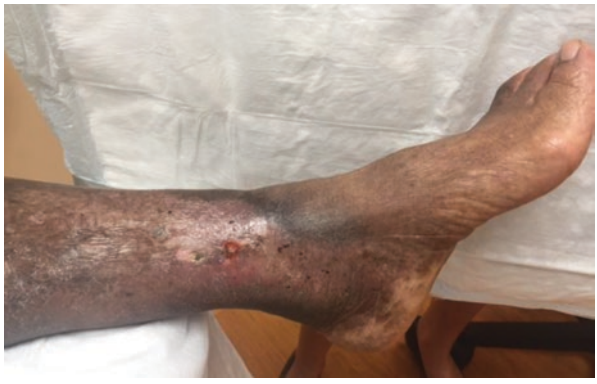

Fig. 2 A small, shallow, moist ulceration can be seen just proximal to the medial malleolus, in the typical "gaiter" distribution described for venous leg ulcers (VLUs)

Assessment and Management

It is important to assess the length, width, and depth of the venous ulcer at each follow-up visit. Additionally, the skin surrounding the wound should be monitored for cellulitis. Measurements and evaluations should take place at regular intervals, using the measurement standards accepted by the individual institution [37].

Edema control accelerates the rate of healing and decreases the chance for recurrence for venous ulcers. Besides external compression, regular exercise, leg elevation for 1 hour daily, and sodium restriction all aid with edema control. In general, 20–30 mmHg knee-high compression is a tolerated and effective means of compression therapy. A review of 39 randomized controlled trials demonstrated that a four-layer bandage system resulted in a significantly shorter time to complete healing than other means of compression for edema control. However, ease of use and patient compliance are often cited as superior with single-layer, knee-high compression stockings [38]. Before adding aggressive compression therapy, adequate arterial circulation should be confirmed, as discussed in the next section on arterial ulcers.

Topical wound dressing choice depends not only on wound characteristics but also on patient and provider preferences. Besides wound healing, the goals of topical wound therapy for venous ulcers should be to maintain a moist healing environment and prevent infection [39]. A Cochrane review of 42 trials revealed that no single topical dressing choice is superior to another, in terms of rate of healing and recurrence of VLU [40]. Table 1 provides a concise review chart for some common topical dressing choices. Healing may be augmented through the use of topical dressings in conjunction with manual debridement by a healthcare professional. Debridement may be discontinued, and topical treatment maintained, once red granulation tissue covers the majority of the wound surface area [41].

Table 1 Some common topical wound dressings

Dressing class	Secondary dressing required?	Dressing frequency	Dressing description	Cost
Hydrogel	Yes	Daily	A gel, maintains moist wound bed, facilitates debridement	$
Hydrocolloid	No	Every 3–5 days	Self-adherent dressing, maintains moisture, occlusive/not to be used if infection suspected	$
Foam	Yes/no	Every 2–3 days	Some brands self-adherent, absorptive, for moderate to heavily draining wounds	$
Alginate	Yes	Every 2–3 days	Ideal for heavily draining wounds: able to absorb 20–30 times dressing weight	$
Saline-impregnated gauze	Yes	Daily or multiple times daily	Maintains moist wound environment, provides some autolytic debridement	$
Collagenase	Yes	Daily	Enzymatically debrides necrotic and nonviable tissue, inactivated by silver-containing products	$$$
Collagen	Yes	Every other day	Promotes collagen matrix formation, works best if wound bed is 90–100% red/granulation tissue	$$

The addition of pentoxifylline or aspirin, either one taken orally on a daily basis, has been demonstrated to be a beneficial adjunct to compression and topical therapy in recent studies. These medications could be considered after a risk-benefit analysis has been performed for the individual patient [42, 43].

Poor prognostic indicators for healing include the following: venous ulcer present for greater than 12 months, diameter larger than 10 cm, or mean wound area reduction ≤30% by week 4 of treatment [35]. To maximize the patient's chance for healing with appropriate treatment, a wound biopsy should be performed on wounds present for longer than 3 months, or for a significantly painful ulcer, in order to rule out malignancy or autoimmune wound subtypes such as pyoderma gangrenosum [44]. Additionally, a referral to a wound specialist should be considered for any venous ulcer failing to diminish in diameter by 30% after a trial of 4 weeks of conventional treatment [45].

Arterial Ulcers

Epidemiology

Peripheral arterial disease (PAD) is present in 18.8% of Americans who are 70–79 years old. Atherosclerosis, calcification, and the resultant arterial narrowing compromise the circulation to the skin over the peripheral digits and limbs. This can result in ulcer formation if left untreated. Male gender, family history, and advancing age are non-modifiable risks for PAD. Smoking, hypertension, hyperlipidemia, and diabetes are other, modifiable risk factors. Also important to recognize is that almost one-third of patients with PAD have concomitant coronary artery disease [46].

Diagnostic Signs and Symptoms

Even prior to ulceration, the patient with PAD may present to the healthcare professional with thin, shiny, and dry skin on the lower extremity. Hair loss on the lower leg, diminished lower extremity pulses, and dependent erythema are also common clinical examination findings. The rule of "5 P's" is an easy way to remember some common findings in the patient with PAD (Table 2).

Lower extremity ulcers of arterial origin are usually located on or near the lateral malleolus or along the distal foot and toes. Sites subject to trauma or friction are often prone to the development of an arterial ulcer.

Arterial ulcers are usually dry and have smooth, even wound margins, giving a "punched-out" appearance. Often, arterial ulcers are covered with a dry, dark or black eschar. In the setting of limb or digit ischemia, these changes may be accompanied by pallor or cyanosis of the digits and/or limb involved (Fig. Fig. 3). In the

Table 2 The "5 P's" of lower extremity arterial insufficiency

Pain	Often severe claudication symptoms described, may change over time
Pulseless	Variable, use Doppler or ABI if suspicion is high
Pallor	Common and not positional in acute ischemia, present mainly on elevation in PAD (with erythema present on leg dependency)
Paresthesia	Complete numbness in acute ischemia, variable in all other PAD patients
Paralysis	A late, poor prognostic sign

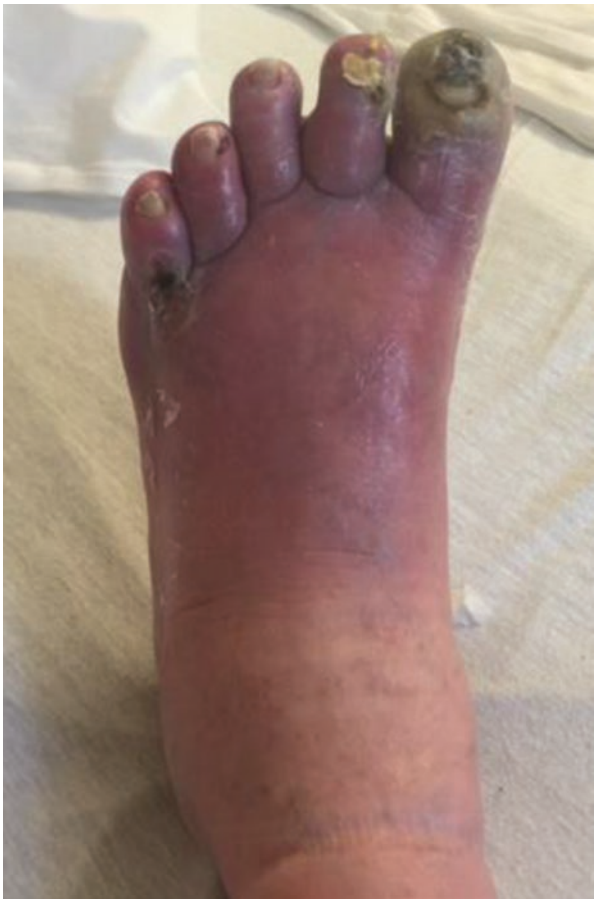

Fig. 3 Arterial ulcerations on the distal great toe, associated with dry eschar and evidence of ischemia, with notable great toe pallor and cyanosis. Additional arterial eschar can be seen on the second, fourth, and fifth toes. Dependent erythema, shiny skin, and thickened toenails are also seen in this patient with peripheral arterial disease

early stages, arterial wound beds are more pale pink, dry, and often deeper than wounds of venous origin. Unlike the mild to moderate pain reported in a venous ulcer, the patient with an arterial ulcer often will report a significant degree of pain. Additionally, the skin surrounding an arterial ulcer is often erythematous, sometimes even in the absence of infection. Nevertheless, vigilance for infection is important, as arterial ulcers are prone to gangrene and overt infection [46].

Table 3 Ankle-brachial index interpretation

ABI result	Interpretation
0.9–1.2	Normal
0.8–1.9	Mild ischemia
0.4–0.8	Moderate ischemia
Less than 0.4	Severe ischemia

Assessment and Management

The presence of pedal pulses is only 26% sensitive in ruling out PAD. An ankle-brachial index (ABI) is a fairly easy and completely noninvasive means of evaluating the patient with suspected PAD. ABI testing can be performed and interpreted by trained clinicians in the office setting but is usually performed in an outpatient radiology or vascular center. The interpretation of ABI results is outlined in Table 3. A normal ABI is 0.9–1.2, and a result less than 0.9 is 95% sensitive and 99% specific at suggesting PAD as a diagnosis. Falsely elevated ABI results can be seen in patients with diabetes as well as in patients with chronic renal disease [47, 48]. A vascular surgery referral is warranted for an ABI result of less than 0.6; the urgency of this consultation increases as the ABI decreases and is dependent on the overall clinical picture. Likewise, external compression therapy should be avoided, pending their vascular surgery consultation, for those patients who have an ABI of less than 0.6 or those who experience an increase in pain with compression therapy [49].

The aims of management for arterial ulcers include pain control, maintenance of a dry and clean wound environment, and consideration for revascularization. It is important to remember the dry wound healing principles used for arterial ulcer treatment are in contrast to the moist healing modalities used in treating a venous ulcer. A dry, clean arterial wound environment should be sustained through the use of daily skin prep application, daily topical iodine, or a simple dry gauze or foam dressing [46]. A recent review of topical treatments for arterial ulcers demonstrated insufficient evidence that any one topical treatment choice results in superior rates of healing [34].

If not contraindicated, antiplatelet medications can be used for the treatment of mild to moderate PAD, to prevent the development of limb ischemia (Table 4). Medical options are also available to aid with controlling claudication symptoms and are most effective when used as part of a regular exercise and smoking cessation program. Of note, cilostazol and pentoxifylline are the only two medications with FDA approval for the treatment of claudication symptoms [50].

The details surrounding surgical revascularization are beyond the scope of this chapter. However, it should be noted that in many cases, an arterial wound will not heal without revascularization. An arterial wound could be considered for manual debridement only after revascularization has been successfully completed, thus minimizing the risk of infection, gangrene, and limb loss associated with debriding an area with inadequate blood supply [46].

Table 4 Antiplatelet agents

Aspirin	Decreases prostaglandin synthesis through inactivation of cyclooxygenase (COX) enzyme
Clopidogrel	Inhibits platelet aggregation by inhibiting adenosine diphosphate (ADP) chemoreceptor on platelet membranes
Dipyridamole	Inhibits platelet aggregation through inhibition of ADP
Ticlopidine	Inhibits platelet aggregation through inhibition of ADP

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Geriatric Dermatologic Disorders

Florence Warren, Danielle Carcia, and Meera Shah

Introduction

The field of geriatric dermatology, or "dermatogeriatrics," will become increasingly important as the geriatric subpopulation continues to grow in the United States and worldwide. There is a limited body of data to guide the evidence-based treatment of geriatric dermatologic conditions due to the frequent exclusion of older adults from clinical trials [1]. In the United States, by 2030, the percentage of the population over 65 years of age will exceed 20%, or over 71 million people [2]. Worldwide, the number of adults over 60 years of age will exceed 2 billion by 2050, or over 20% of the world's population [3]. This chapter will review the various common geriatric dermatoses including benign skin eruptions, inflammatory conditions such as xerosis and pruritus, cutaneous autoimmune disorders, and vascular disorders, as well as give a brief overview of dermatophyte infections, viral infections, and premalignant lesions.

Skin changes associated with aging can be classified into two groups: intrinsic and extrinsic age-related changes. Intrinsic aging includes changes associated with normal maturity that occur in all individuals due to genetics, epigenetics, and physiology. Extrinsic aging includes changes which occur due to exposure to environmental factors such as ultraviolet light and smoking [1]. Skin aging results from a combination of factors including physiology, genetics, and environmental factors.

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Treating common geriatric dermatologic conditions requires a basic understanding of the major changes in skin function associated with aging. These changes include epidermal barrier defects, immunosenescence, and altered wound healing capacity [1]. Basic examples of these age-related changes include progressive thinning of the epidermis, decreased cell replacement of the epidermis, increased blood vessel fragility, and dryness. The number of melanocytes, fibroblasts, and Langerhans cells is reduced which causes various changes in skin pigmentation, elasticity, and barrier function [4]. Several molecular changes occur which alter the ability of the skin to mount an immune response and mediate self-repair [1]. All of these changes contribute to various skin disorders in the geriatric population which often impact quality of life and produce significant morbidity and mortality [4].

Autoimmune Disorders

The aging process is associated with waning cutaneous immunity as a result of intrinsic and extrinsic degeneration of immune function. The development of cutaneous immune dysfunction may result in several disorders including bullous pemphigoid, mucous membrane pemphigoid, pemphigus vulgaris, paraneoplastic pemphigus, and lichen sclerosus.

Bullous Pemphigoid

Bullous pemphigoid is an autoimmune blistering disease that results from the presence of tissue antibodies to hemidesmosomal proteins present in the basement membrane of stratified squamous epithelia [5]. The presence of these antibodies ultimately results in the separation between the dermis and the epidermis and the formation of bullae [6]. This disease typically occurs in patients older than 60 years of age, and the incidence is similar in men and women [5, 7]. Bullous pemphigoid is a chronic eruption characterized by multiple bullae on normal skin or on an urticarial base. Lesions typically occur on the trunk or extremities, but localized presentations can also occur [8] (Fig. 1). Patients may present with intense pruritus and hives initially. The blisters of bullous pemphigoid are typically large tense blisters resistant to minor trauma. The diagnosis is confirmed with histology, immunofluorescence microscopy, and molecular biology techniques [7]. First-line treatment of bullous pemphigoid includes high potency topical corticosteroids [6, 8]. Additional immunomodulatory therapies including azathioprine, mycophenolate, methotrexate, and tetracycline with

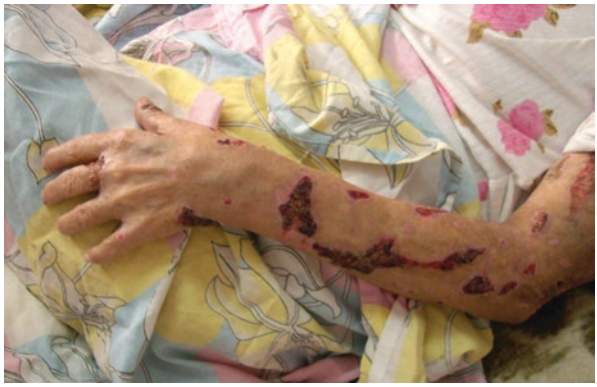

Fig. 1 Bullous pemphigoid. (WikiCommons by Ashashyou—Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=42563781)

nicotinamide may be necessary if therapy is required long term to reduce the long-term effects of corticosteroid use [5, 6, 8].

Mucous Membrane Pemphigoid

Mucous membrane pemphigoid is a rare, chronic, autoimmune blistering disease that affects the mucosal surfaces of the mouth, eyes, nose, oropharynx, esophagus, and genitals. In 20–30% of patients, blisters can occur on the head, neck, and upper trunk [6]. Recognizing this diagnosis is important as mucous membrane pemphigoid may cause significant morbidity due to tissue destruction. The diagnosis is confirmed with histology, immunofluorescence microscopy, and molecular biology techniques [7]. Complications may include blindness due to occlusion of lacrimal ducts which can lead to optic keratitis [5]. Patients diagnosed with mucous membrane pemphigoid should be referred to an ophthalmologist promptly for evaluation. The first-line treatment includes high potency topical steroids; however patients may require systemic immunomodulators to control inflammation and prevent progression and complications from this disease [5].

Pemphigus Vulgaris

Pemphigus vulgaris is the most common and most serious of the autoimmune blistering disorders [7]. Pemphigus vulgaris typically occurs between the ages of 50 and 65 years, and many cases have been described in the geriatric population [7]. Pemphigus vulgaris is characterized by histological acantholysis (loss of cell-to-cell adhesion) and mucosal (Fig. 2) or cutaneous blistering. Intraepidermal blistering

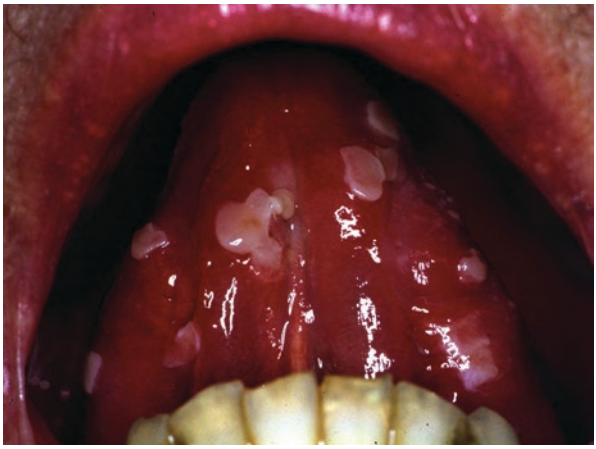

Fig. 2 Mucosal pemphigus vulgaris. (DERMNET NZ)

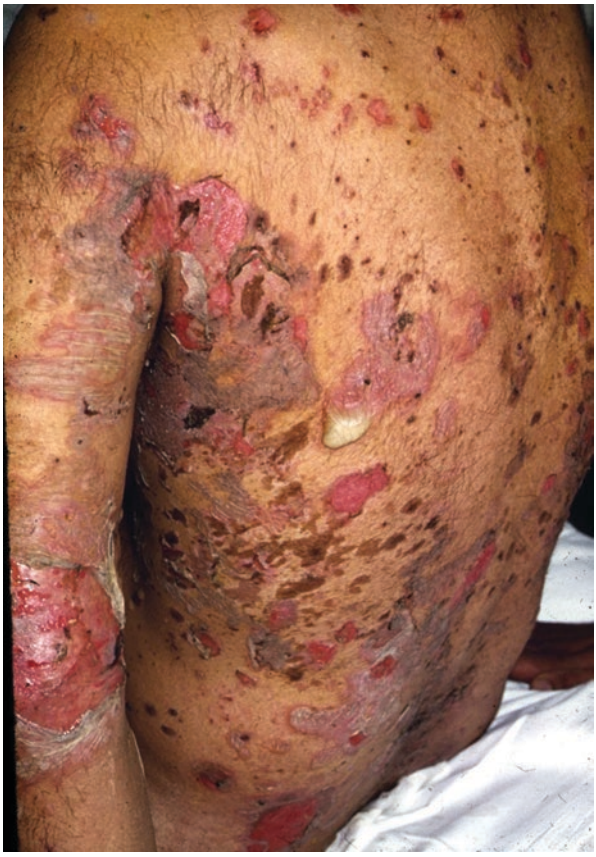

Fig. 3 Pemphigus vulgaris. (DERMNET NZ)

observed in pemphigus occurs due to an immune response that results in the deposition of autoantibodies against epidermal cell surface antigens within the epithelium of mucous membranes or the skin [7]. Blisters initially present in the mouth and are followed by blistering of the trunk, limbs, face, and scalp, and lesions progressively ooze and become crusted over (Fig. 3). Nikolsky's sign is typically present and can aid in the diagnosis, in which lateral pressure to the edge of the blister produces an erosion [5]. The diagnosis is confirmed with histology, immunofluorescence microscopy, and molecular biology techniques [7]. Pemphigus vulgaris requires prompt treatment as failure to treat may result in electrolyte imbalance of secondary infection. First-line treatment includes systemic corticosteroids; however patients may require systemic immunomodulators to prevent the progression of this disease [5, 9].

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is a mucocutaneous blistering disorder which typically occurs in patients older than 60 years of age in association with leukemia, lymphoma, Castleman's disease, and thymoma, among other diseases [7]. The pathophysiology is not well understood; however it is also thought to be secondary to an autoimmune etiology [7]. This disorder occurs twice as often in men than in women. Paraneoplastic pemphigus is characterized by painful mucocutaneous erosions which typically begin in the oral mucosa. Flaccid or tense bullae, lichenoid papules or plaques, targetoid lesions, and erosions are associated with this disorder. The treatment of paraneoplastic pemphigus is similar to that of the other autoimmune blistering conditions [7].

Lichen Sclerosus

Lichen sclerosus is an autoimmune condition that affects the genital skin, more commonly in women but can also occur in men. Lichen sclerosus is characterized by well-demarcated, white papules and plaques which can occur throughout the genital area (Fig. 4) but most commonly occurs on the labia in women [10]. The primary symptom associated with this condition is pruritus, and this may lead to lichenification. This condition may result in rare but serious complications which include significant scarring and adhesions which narrow the introitus [5]. This may lead to difficulty with urination and dyspareunia [5]. Lichen sclerosus is also associated with an increased incidence of invasive squamous cell carcinoma in the anogenital area, and it has not been established if this is related to treatment [10]. First-line treatment of lichen sclerosus includes high potency corticosteroids such as clobetasol [5].

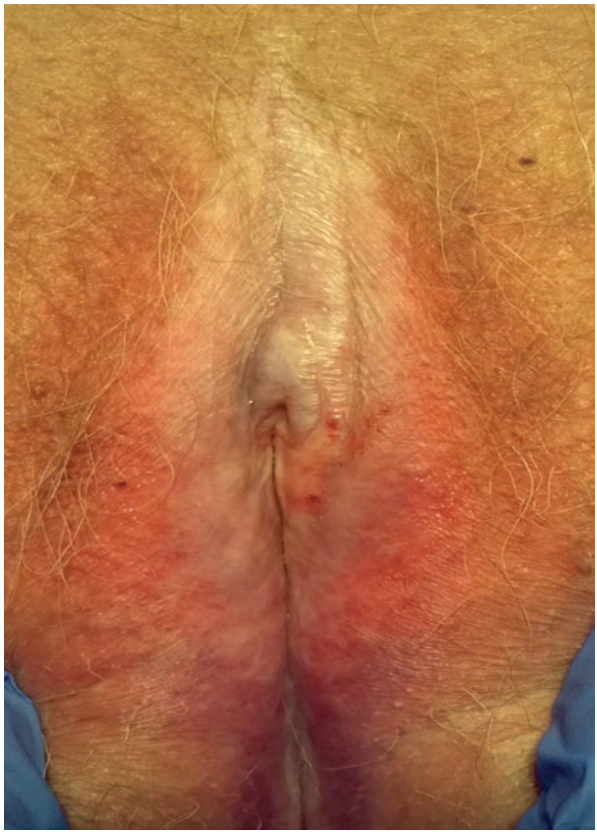

Fig. 4 Lichen sclerosus. (By Mikael Häggström—Own work, CC0, https://commons.wikimedia.org/w/index.php?curid=34245139)

Viral Infections

Herpes Zoster and Postherpetic Neuralgia

Herpes zoster (shingles) occurs with the reactivation of varicella zoster virus. Over two thirds of cases occur in patients older than 50 years of age, and the condition is most commonly seen in patients older than 60 years [5]. Certain risk factors, most likely reduced cell-mediated immunity to varicella zoster virus with advancing age, may reactivate the virus [11]. Shingles is characterized by a vesicular eruption on an erythematous base that occurs in a unilateral, dermatomal distribution (Fig. 5).The most common site is the thoracic dermatome (>50%) followed by the trigeminal dermatome (10–20%) [11]. The rash may be preceded by a prodromal tingling or itching sensation [11]. The vesicular rash eventually crusts over and may last for up to 2 weeks. Herpes zoster is usually self-limiting but can be serious in immunosuppressed patients and when there is optic nerve involvement. Treatment of herpes zoster includes antivirals such as acyclovir which should be initiated within 72 hours if possible to prevent potential complications and sequelae. Postherpetic neuralgia

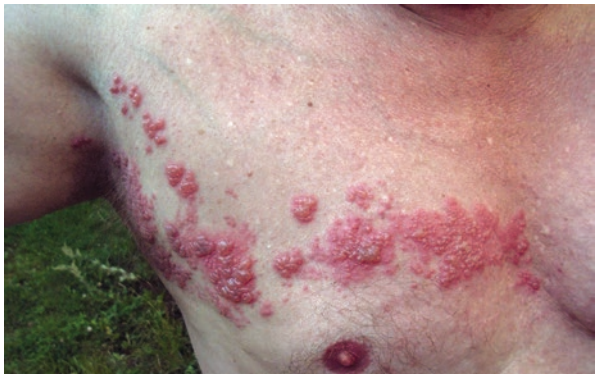

Fig. 5 Herpes zoster. (By Fisle—Fisle, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=2558194)

occurs in approximately half of patients with herpes zoster reactivation older than 60 years, and the risk for development of this complication increases with age [5]. Postherpetic neuralgia can be avoided by treating the reactivation promptly with antiviral medications. Prompt initial treatment significantly reduces the severity of pain during the reactivation as well as the risk of developing postherpetic neuralgia, especially in the geriatric population [5]. Zoster vaccine (Zostavax) may be used for prevention as this vaccine decreases the incidence and severity of viral reactivation [6].

Inflammatory Dermatoses

Inflammatory dermatoses are a common condition among our elderly population. As our population ages, a decreased hydration status and epidermal water losses lead to pruritus which causes the person to scratch. Additionally, a decrease in sweat glands and their activity lead to dry skin. This then leads further to an inflammatory reaction and cycle, leaving the skin irritated, cracked, and dry and therefore susceptible to infection and further irritation [12].

Asteatotic eczema is a very common skin disorder in the elderly which goes by many names including eczema craquelé, senile pruritus, or simply xerosis. It is most common in the winter months when dry heat and cold weather are more common. The most likely affected area is the lower legs, but nearly any area may be affected by this condition (Fig. 6). The most mild form includes dry skin changes which can progress to flaking and cracking in more severe cases. Fine red plaque may form along the cracks and leave the skin prone to infection. Treatment modalities focus on prevention and healing with moisturizing creams and gentle soaps and by avoiding rubbing or picking. If conservative measures fail to resolve the xerosis, a steroid (class II–XI) may be used sparingly. Once the xerotic cycle is stopped, continued hydration and avoidance of harsh irritants should be followed to prevent reoccurence [1]. If extensive or widespread eczema craquelé is seen, underlying causes such as lymphoma should be ruled out [6].

Contact dermatitis is prevalent in the elderly population despite the decreased ability to mount a type IV sensitivity reaction [13].

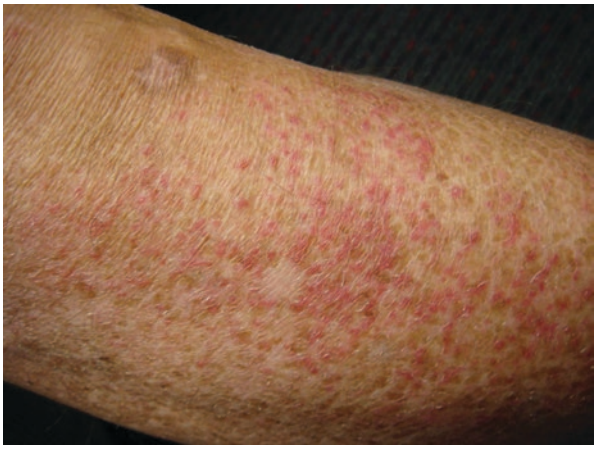

Fig. 6 Asteatotic eczema. (DERMNET NZ)

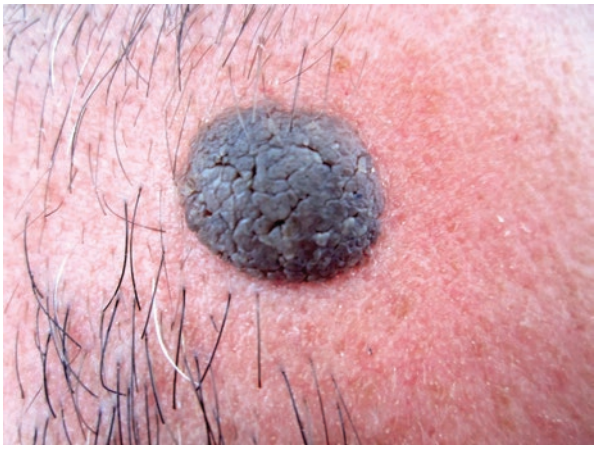

Fig. 7 Seborrheic keratosis. (WikiCommons)

Benign Skin Eruptions

Seborrheic keratoses are very common lesions in the elderly and increase with age. It appears as a brown, stuck on lesion varying in size and shape (Fig. 7). They are most common on the trunk and back but may occur nearly anywhere on the skin. Treatment is not necessary except for cosmetic reasons. If suspicion for malignant lesion exists, a biopsy should be considered [14].

Acrochordon is a painless, benign, flesh-colored skin lesion which arises in people of all ages but may be more common after age 40 (Fig. 8). They most commonly are located on the head and neck. Rarely, basal cell carcinoma may arise from an

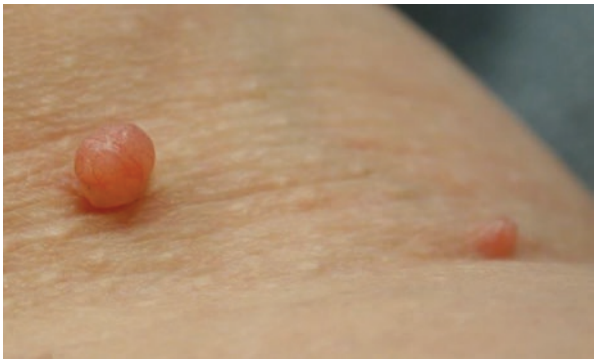

Fig. 8 Acrochordon. (WikiCommons)

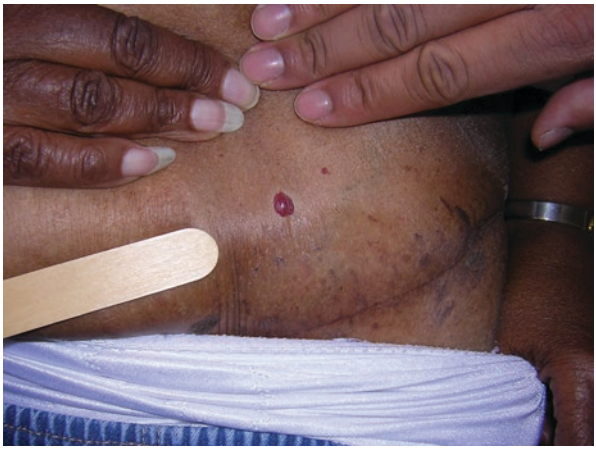

Fig. 9 Cherry angiomas. (James Studdiford/Thomas Jefferson University)

acrochordon [11]. Treatment is via surgical excision and is for cosmetic reasons only unless a concern for underlying malignancy exists.

Cherry angiomas are reddish-purple papular lesions typically small (1–3 mm) in size which begin at age 30 and increase with age (Fig. 9). They are formed from dilated capillaries and are completely benign. Treatment is not necessary except for cosmetic purposes and may be achieved by laser or electrocoagulation [15].

Dermatosis papulosa nigra is a subtype of seborrheic keratosis seen most prominently in dark-skinned elderly individuals (Fig. 10). The condition is classified by pigmented smooth papules ranging from 1 to 5 mm in size typical in a distribution on the head and neck [16]. Typically they are numerous and may continue to become more numerous with aging. Treatment options are for cosmetic purposes only but may include electrodesiccation, cryosurgery, shave removal, or laser. There may be undesirable outcomes including scarring, hypopigmentation, or hyperpigmentation in resultant areas [17].

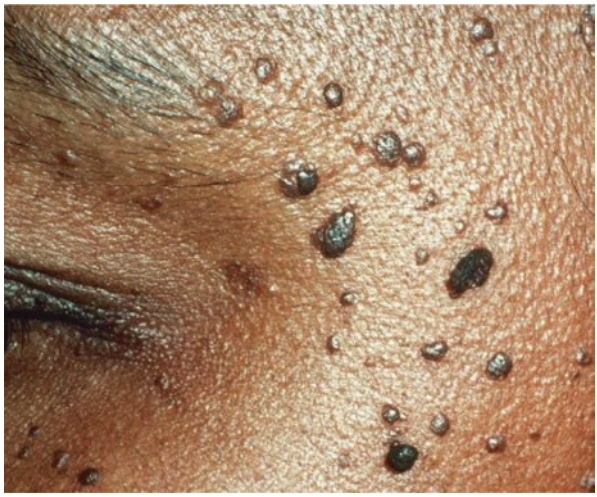

Fig. 10 Papulosa nigra. (WikiCommons)

Drug Eruptions

Polypharmacy and drug metabolism are important concepts when caring for the elderly population. Due to alteration in hepatic and renal function and numerous medications, elderly patients are at increased risk for reactions from and interactions between their medications. The manifestation of these reactions may vary greatly but generally are of a few different varieties: maculopapular, morbilliform, vasculitis which is associated with systemic symptoms such as fever and fatigue, contact dermatitis (for topical creams and ointments), and photosensitivity. A fixed drug eruption may present in the same area each time the patient uses a particular medication or class of medications. They typically appear as erythematous round lesions and are typically single (Fig. 11). Erythema multiforme is a drug reaction not exclusive to the elderly but nonetheless important due to its very serious severe reaction which if systemic symptoms exist may lead to Stevens-Johnson syndrome or toxic epidermal necrosis. Erythema multiforme often initially presents with target-like lesions on the trunk and upper or lower extremities. A history is imperative when diagnosing a possible drug eruption including the timing of new medication initiation and all other medications the patient may be taking such as over-the-counter vitamins. Treatment focuses on stopping the causative agent and future avoidance of this medication or others in its class [6].

Vascular Disorders

Decubitus (pressure) ulcers are an unfortunate consequence common but not exclusive to our elderly population. Limited mobility, incontinence, poor nutrition, and immunosuppression all play a role in susceptibility to pressure wounds. They are most common

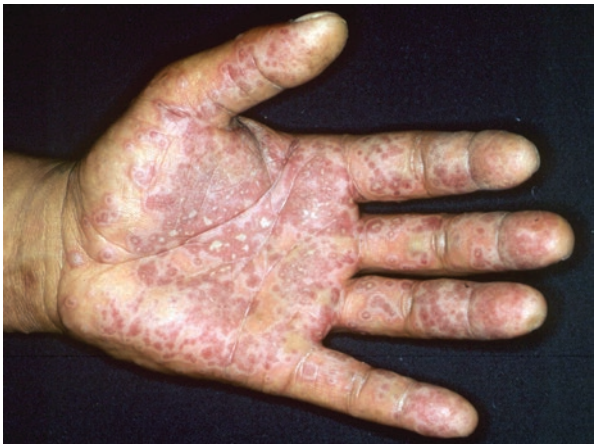

Fig. 11 Erythema multiforme. (WikiCommons)

over bony prominences but may occur anywhere that the skin is exposed to a prolonged position without change. There are four stages to pressure wounds. Stage I consists of non-blanchable erythema with underlying intact skin. Stage II pressure ulcers are defined by open skin, with involvement of the epidermis and dermis. There may be areas of necrosis. Stage III pressure ulcers have extension to the fascia but not to underlying tissues, and Stage IV pressure ulcers extend to the underlying muscle or bone. A pressure ulcer may be characterized as unstageable if there is an overlying eschar which prevents visualization into the wound bed. The treatment of pressure ulcers ideally begins with prevention and consistent offloading of the pressure ulcer site. Once a pressure ulcer is present, the treatment varies widely based on the stage. No matter what stage, the area must be offloaded with close attention to prevent another pressure ulcer at a different location. Proper nutrition and hydration will also aid with healing. Additionally, various different techniques may be used depending on the wound such as simple cleansing and covering to chemical or surgical debridement [6].

Stasis dermatitis is a common skin disorder seen in persons with impaired venous drainage. The hallmark of the condition is a stigmata of changes in the skin associated with known venous drainage problems and varicose veins (Fig. 12). The affected may experience intense pruritus, along with xerosis (dry skin), or have a weeping and wet appearance. Treatment is essential to preventing further skin breakdown and venous ulcers. Treatment is focused on applying external pressure to aid the venous congestion in draining such as using wraps or compression stockings. Additionally, elevation of legs with frequent dorsiflexion of the foot is helpful in draining the venous system effectively [6].

Purpuric lesions are common in the elderly due to the fragility of the skin and underlying blood vessels [6]. The etiology of purpura may be from thrombocytopenia, decreased skin elasticity, vascular defects, trauma, or drug reactions [14]. Common medications that may cause purpura include penicillin, quinine, and heparin [6]. Spontaneous purpura may happen in the elderly population and can often be complicated by skin tears [14]. Skin health and integrity must be maintained to prevent bleeding, including hydration, good nutrition, and moisture.

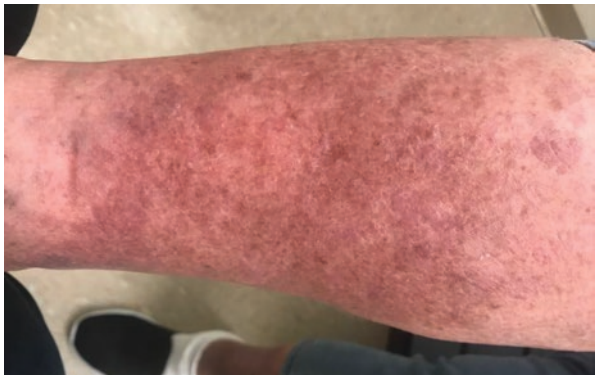

Fig. 12 Stasis dermatitis. (J Russell)

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