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Differin® Lotion, 0.1% is indicated for the topical treatment of acne vulgaris in patients 12 years and older. A thin film of Differin® Lotion, 0.1% should be applied once per day to the face and other areas of the skin affected by acne. In clinical trials, the most common adverse event (>1%) reported with use of Differin® Lotion, 0.1% was mild to moderate skin dryness. Erythema, scaling, stinging and burning may also occur. Excessive exposure to sunlight and sunlamps should be avoided during treatment, and use of sunscreen products and protective clothing is recommended. Concomitant use of drying or irritating topical products (like products containing resorcinol, salicylic acid or sulfur) should be used with caution. Instruct patients to avoid the eyes, lips and mucous membranes when applying Differin® Lotion, 0.1%, and not to apply to areas that have been depilated with wax products. Differin® Lotion, 0.1% has not been tested in pregnant or nursing women, or with the elderly. Pregnancy Category C.

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BRIEF SUMMARY
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DIFFERIN Lotion is a retinoid product indicated for the topical treatment of acne vulgaris in patients 12 years and older.

CONTRAINDICATIONS
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WARNINGS AND PRECAUTIONS
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DRUG INTERACTIONS
Concomitant use of topical products with a strong drying effect can increase skin irritation. Use with caution, especially in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN Lotion. Wax depilation should not be performed on treated skin.

Pregnancy
Pregnancy Category C. There are no well-controlled trials in pregnant women treated with DIFFERIN Lotion. Therefore, DIFFERIN Lotion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal reproduction studies have not been conducted with DIFFERIN Lotion. Furthermore, such studies are not always predictive of human response.

Human Data
In clinical trials involving DIFFERIN Lotion, 0.1% in the treatment of acne vulgaris, women of childbearing potential initiated treatment only after a negative pregnancy test. Two women became pregnant while using DIFFERIN Lotion, 0.1%. One patient delivered a healthy full term baby and the other patient electively terminated her pregnancy.

Animal Data
No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day, up to 25 times (mg/m²/day) the maximum recommended human dose (MRHD) of 2 grams of DIFFERIN Lotion. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of ≥ 25 mg adapalene/kg/day representing 123 and 246 times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele and skeletal abnormalities in rats; and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in rabbits. Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg adapalene/kg/day [25-59 times (mg/m²) the MRHD] exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits. Systemic exposure (AUC 0-24h) to adapalene at topical doses (6.0 mg/kg/day) in rats represented 101 times the exposure to adapalene in patients with acne treated with DIFFERIN Lotion applied to the face, chest and back (2 grams applied to 1000 cm² of acne-involved skin).

Nursing Mothers
It is not known whether adapalene is excreted in human milk following use of DIFFERIN Lotion. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Lotion is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of DIFFERIN Lotion in pediatric patients under the age of 12 have not been established.

Geriatric Use
Clinical studies of DIFFERIN Lotion did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity, mutagenicity and impairment of fertility studies were conducted with DIFFERIN Lotion.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m²/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m²/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 times (rats) the MRHD of 2 grams of DIFFERIN Lotion. In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed. No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g. retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects in vitro (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) or in vivo (mouse micronucleus test).

In rat oral studies, 20 mg adapalene/kg/day (120 mg/m²/day; 98 times the MRHD based on mg/m²/day comparison) did not affect the reproductive performance and fertility of F0 males and females, or growth, development and reproductive function of F1 offspring.

PATIENT COUNSELING INFORMATION
• Apply a thin film of DIFFERIN Lotion to the affected areas of the skin once daily, after washing gently with a mild soapless cleanser. Dispense a nickel size amount of DIFFERIN Lotion (3-4 actuations of the pump) to cover the entire face. Avoid application to the areas of skin around eyes, lips and mucous membranes. DIFFERIN Lotion may cause irritation such as erythema, scaling, dryness, stinging or burning.
• Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply DIFFERIN Lotion to the entire face or other affected areas as a thin layer, avoiding the eyes, lips and mucous membranes.
• Exposure of the eye to this medication may result in reactions such as swelling, conjunctivitis and eye irritation.
• Patients should be advised not to use more than the recommended amount and not to apply more than once daily as this will not produce faster results, but may increase irritation.
• Advise patients to minimize exposure to sunlight including sunlamps.
• This medication should not be applied to cuts, abrasions, eczematous, or sunburned skin.
• Wax depilation should not be performed on treated skin due to the potential for skin erosions.

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A New Tretinoin Therapy
From Triax Pharmaceuticals
SOME years ago, the American Cancer Society first mounted a campaign against modesty to publicize the need for breast examinations. All too often, women were not only too embarrassed to let their physicians fully examine their chests, but they were also reluctant to perform self-examination.

This was not the case of the young woman who presented with a black lesion on her right breast. She was concerned about the peculiarity of the lesion since its appearance 2 months prior (Figure). Fortunately, modesty did not play a role in her situation. The lesion was quickly excised and proved to be a level 3 melanoma. How many other patients are not so fortunate to have appropriate removal and treatment before it is too late?

CANCER SCREENING

Americans should be well informed on the importance of early detection in skin cancer. Much emphasis has been placed on this concept; however, while patients may be attuned to the idea of cancer screening for other body systems, they do not grasp the concept of the full body scan. This diagnostic procedure, needless to say, cannot be accomplished in a proper fashion without disrobing, but many patients are reluctant to do so.

As any seasoned clinician can attest, melanomas and nonmelanoma skin cancers can be found in any area of the body from the breasts to the soles. They do not avoid the genitalia, let alone the intertriginous areas. Curiously, primary cutaneous melanomas in hidden anatomic sites are thicker than those in visible sites, likely because of a delay in diagnosis.1,2 Additionally, the problem may be compounded by UV radiation from indoor tanning. Many a tanner disrobes completely to obtain his or her money’s worth at the tanning parlor but is reluctant to have the dermatologist see most of the body.

MODESTY AT WORK

Let’s reflect upon the skin examination. Isn’t its purpose to find anything that might create a problem? The reason for the procedure is to examine visually every skin surface. The act of wearing any clothing only serves to hinder and prolong the examination.

Modesty is a behavior, manner, or appearance intended to avoid impropriety or indecency. During a physical examination, modesty is not serving to avoid impropriety or indecency. It is a false modesty. Much like the modesty panel underneath a desk or nude-colored hosiery worn by women, it is a social construct. The impropriety and judgment felt by the patient and others is also created by society.

The subject of modesty has been examined in detail in other disciplines. For example, one such study on modesty sought to explore the role that culture played, finding that some perspectives on modesty are accounted for by culture, while others are not.3 Modesty was found to be driven by maturity/age, religion/culture, or esteem/upbringing. For the maturity-driven group, modesty did not play a role in the health care setting, while the religiously/culturally driven group felt modesty should be considered in a health care setting. (Disrobing in this setting was not an issue.) Most interestingly, the esteem-driven group posed the greatest challenge to health care providers, as this group felt it stressful and uncomfortable to undress in the health care setting and would likely avoid screening for reasons of modesty.

Although not formally studied, one realizes that body image plays a large role in patient modesty. Patients worry that as the physician examines their skin they are secretly being judged on their lingerie or less-than-ideal body weight. Here, the truth hurts—the clinicians are doing their job—to screen the patient for skin cancer.

There are many papers detailing ways to protect patient modesty,4–8 but just as important as the patient’s comfort is the necessity to perform a thorough examination. The most obvious way to accomplish an appropriate examination to detect malignancy, including the scalp, oral cavity, genitals, and nails, would be disrobing.9 The patient may wear a gown to cover surfaces not being examined. An alternative involves the patient disrobing one quadrant at a time. It is both curious and unfortunate when a patient requests a full body scan but only permits limited views of the skin.

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REFLECTIONS

When reflecting upon the situation, the role of modesty in prophylactic screening is raised. What stands out is a lack of compliance in both breast and colon cancer screening due to modesty.10,11 If patients are unwilling to undergo cancer screening developed for the sole purpose of early detection and prevention, we can only conclude that modesty should be considered dangerous to their health.

Skin self-examination is one method that might prove an alternative for those too modest to allow yearly examination of the entire skin’s surface. Self-examination taught to both patient and partner improves self-efficacy for patients.12

Partnering with those trusted by the patient might improve detection and outcomes for patients too modest for frequent skin examination.

Isn’t there an old adage: Modesty killed the cat?

REFERENCES

The venereal form of treponematosis, caused by the spirochete Treponema pallidum, plagued every major city in the preantibiotic era. “Civilization means syphilization,” was an idea touted by Richard von Krafft-Ebing in the late 19th, and early 20th centuries that the effects of modern life make men more susceptible to syphilis and other diseases. Christopher Columbus was thought of as an importer of syphilis to Europe. Because his serendipitous voyages to the New World initiated the process of Spanish colonization, which foreshadowed general European colonization of the New World, it is difficult to rule out the cultural and political animosity created by Columbus and his men. These recent revelations are intriguing and may create dialogue that may subsequently challenge the age-old theory of “East to West” spread of venereal syphilis. This contribution warrants the continuation of study in this direction, taking into account skeletal studies that utilized radiocarbon dating technique and the phylogenetic analysis of the bacterial strains, offering a possible consensus on the origin and evolution of syphilis.

Syphilis, a treponemal disease, has undergone discernible metamorphosis in its natural history. The diverse clinical manifestations of syphilis are known to masquerade as a spectrum of clinical entities, earning itself the reputation of being the great imitator. Syphilis was even mentioned in Act 3 of Timon of Athens by William Shakespeare:

Live loathed and long,
Most smiling, smooth, detested parasites,
Courteous destroyers, affable wolves, meek bears,
You fools of fortune, trencher-friends, time’s flies,
Cap and knee slaves, vapours, and minute-jacks!
Of man and beast the infinite malady
Crust you quite o’er! What, dost thou go?
Soft! take thy physic first—thou too—and thou;—
Stay, I will lend thee money, borrow none.

The name for syphilis is derived from Fracastorius’ 1530 epic poem in three parts, Syphilis sive morbus gallicus (“Syphilis or The French Disease”), about a shepherd boy named Syphilus who insulted the sun god of Haiti and was punished by that god with a horrible disease. The poem suggests using mercury and “guaiaco” as a cure. Oil of guaiac is a fragrance used in soap, originating from the Palo Santo, sacred tree in Ecuador, which provides an essential oil that heals both body and spirit. Syphilis, with its antiquity, has carried social stigma. In order to avoid the cultural embarrassment, countries attempted “to pass the buck to others.” Accordingly, variations in its nomenclature were likely; the English and the Germans called it the “French disease”; the French called it the “Neapolitan sickness”; the Russians, the “Polish sickness”; the Poles, the “German sickness”; Flemish, Dutch, Portuguese, and North Americans called it the “Spanish sickness” or “Castilian sickness”; and the Japanese, the “Canton rash” or “Chinese ulcer.” The term Great pox was used for 2 centuries to differentiate syphilis from Smallpox.

Christopher Columbus, the great Italian voyager, whose precise date of birth is only speculated, left on his first voyage at the age of 41 years (1492–1493). His journey initiated the process of Spanish colonization, which foreshadowed the general European colonization of the “New World.” The idea that “Civilization is Syphilization” has historically stamped Columbus as the importer of syphilis to Europe. The current contribution attempts to review the more recent archeological reports, dendrochronologic findings, and radiocarbon dating studies in order to clarify the development of the disease. The origin and evolution of syphilis is currently unknown and may continue to puzzle researchers until a plausible consensus is developed.
HYPOTHESIS OF THE ORIGIN OF SYPHILIS

THE UNITARIAN THEORY

Hudson12 has been credited with the unitarian theory, which claims that treponemal diseases originating from one form, free-living treponemes in the mud, ultimately evolve into human saprophytes. “Yaws” appears to have first evolved in Central Africa, from where it spread to engulf the east and north, probably attributable to the importation of slaves to Egypt in 30th century BCE.13,14 Yaws eventually spread to the Arabian Peninsula and the valleys of the Tigris and Euphrates rivers, where it was called Bejel.15 Dissemination of yaws into Europe followed, peaking in the 8th century CE, when the Crusades made the slave trade from Africa more popular by transporting slaves for work to other countries.16,17 The Crusades moved from Europe to the Holy Land between the 11th and 14th centuries.

It was between the 17th and 19th centuries that a series of yaws-like diseases, the endemic syphilis, and pinta were identified in individuals who had a poor rural background and overcrowded living conditions. Endemic syphilis prevailed as the Spirocolon of Greece, the hills of Bosnia, the Pian of Nerac in South-West France, the Button scurvy of Ireland, the Sibbens of Scotland, the Radseyge of Scandinavia, Siti of Gambia, Therlijevo of Croatia, Njovera of Zimbabwe, Frenjak of the Balkans, and nonvenereal endemic syphilis, Bejel disease. The Dithmarsh evil of Jutland and Schlesweig-Holstein is yet another entity. All of these diseases, including yaws, were considered to be a consequence of either direct or indirect social contact, affecting all age groups. Children and family members were the most susceptible.

The histories of Button scurvy and Sibbens have also been documented.18,19 These entities have been defined and classified into endemic syphilis or treponarids, and are considered to be a form of yaws modified by climatic conditions, clothing customs, and even the sharing of drinking utensils. This seems plausible due to the fact that yaws was later shipped via slaves from West Africa to the West Indies. In addition, some treponemes adapted to the conditions by thriving in the moist and warm areas of the body and by mutating into more lethal organisms. The latter was acquired by sexual contact and expressed as syphilis in the contemporary context.

In the absence of any viable means to control the transmission of treponemes, the advent of soap in the Arab peninsula and Europe in the 7th and the 14th century, respectively, and its widespread use was acknowledged as a possible mode for the reduced survival of treponemes in treponarids.

NONUNITARIAN THEORY

An African origin hypothesis developed, with endemic treponemes originally acquired from apes, brought back to Europe by the Portuguese during the Age of Exploration.6

Another theory for the post-1492 syphilis outbreak mentions the role of a human immunodeficiency virus–like immunosuppressive agent causing an uncharacteristically severe variant of syphilis, lues maligna.

PRE-COLUMBIAN PERCEPTION

The perception that treponemal infection existed in the pre-Columbian civilization, which is now the southwestern part of the United States, was documented by the lesions indicative of treponematosis in a burial site found in the central Great House of Chaco Canyon, Pueblo Bonito, New Mexico, an epicenter of a broad culture system that spanned the Four Corners regions, in contrast to numerous reports available from New World skeletal burial remains. This is an interesting revelation, which may open a venue for future workup.20–24

COLUMBIAN THEORY

It is speculated that treponematoses was absent in Europe in the pre-Columbian era until the 13th century CE, when yaws appeared as a possible result of slave trading.26 Berbers and Moors, from North and North-West Africa, established themselves in Southern Europe, mostly in Spain, in the 15th century. Half a century prior to Columbus’ first voyage (1492–1493), Spanish and Portuguese sailors already competed with more extensive journeys down the West coast of Africa and encouraged the migration of the Africans.

Despite the efforts for quarantines, yaws spread to the European continent. According to the Columbian theory, venereal syphilis appears to have been brought from the New World and joined so-called endemic syphilis. An outbreak of the epidemic resurfaced upon the return of Columbus and his men from the New World. A similar presentation of the disease was identified in the indigenous people of the New World as well as in the members of Columbus’ crew. The epidemic in the earliest years, popularly called the Morbus gallicus, may have been the combination of 2 diseases; the newly arrived sexually acquired venereal syphilis and the old socially acquired endemic syphilis forms of yaws.19

The changes in clinical presentation, particularly in the first half of the 16th century, might be the result of expanding influences of the Renaissance, including improved personal hygiene. Others explain the devastating Morbus gallicus as the relatively benign venereal syphilis of the New World, afflicting people with no previous contact with the condition and producing more
obvious signs and symptoms, both the views commensurate with the Columbian theory. Accordingly, the arguments for and against the Columbian theory are listed below.

- Syphilis, as one form of pathologic treponematosis, has a skeletal signature. Rothschild demonstrated that the osseotype characteristics of syphilis were absent in specimens from pre-Columbian Europe, Africa, and Asia. The absence of evidence for congenital transmission of syphilis is critical in understanding the nature of the disease. Syphilis, as one form of pathologic treponematosis, has a skeletal signature. Rothschild demonstrated that the osseotype characteristics of syphilis were absent in specimens from pre-Columbian Europe, Africa, and Asia.27

- The sailors with Columbus in 1493 were said to have brought the disease back to Spain. The Spanish fleet, when they fought for King Alfonso II against the French forces of Charles VIII of France in 1494–1495, heavily infected the people of Naples. The illness spread rapidly around Europe and mercenaries, who in 1496 joined Perkin Warbeck in Scotland and with the support of James IV of Scotland, invaded England, bore both arms and the grandgore (Old French; grand gorre: grand = great + gore = syphilis), as it was then called. In 1497, the Minutes of the Town Council of Edinborough (Phil. Trans. XLII. 421) recognized: “This contagious sickness call it the Grandgore.”28

- The osseous evidence documents the presence of syphilis in Hispanola, where Columbus landed. Columbus’ crew had the opportunity and means to contract and spread this venereal disease.27

- In the work “Tractado contra el mal serpentino,” written in 1510 and published in 1539, Ruy Diaz de Isla had been thought to have cured, during the travel of return in Europe, many members of the crew of Columbus, affections from certain luetic manifestations, and thought that the new disease was imported from Hispanola. This view was supported by Bartolomè de Las Casas.29

- The absence of evidence for congenital transmission of the disease in pre-1492 North America suggests that this treponemal disease was not the same venereal form we know today.30

CONTEMPORARY SCENARIO

Several archeologic studies have taken cognizance of phylogenetically diverse material at different geographic locations and have gathered together enough evidence to suggest that the disease existed in Europe, long before the birth of Columbus (October 31, 1451–May 20, 1506).31 The osseotype characteristics of syphilis are absent in specimens from pre-Columbian Europe, Africa, and Asia.32

A study was conducted on approximately 240 skeletons exhumed at the site of a medieval friary in Hull. The skeletons were mostly of Augustinian friars, Mendicants serving the local poor, and seamen and prostitutes. Of the 245 well-preserved skeletons found, 207 were relatively complete. Many were buried in wooden coffins, prepared from the wood brought from the Baltic countries. Dendrochronologic examination indicated that the trees had fallen between 1340 and 1369. The interpretation of the findings was, therefore, found to be confusing. Three skeletons showed more variable and more widespread bony lesions. One of these three, number 1216, was that of a man aged between 25 and 35 years. He showed signs of syphilitic stigmata: thickening with areas of localized disease of thigh bones, sabre-like thickening of shin bones, perforation of the palate, and erosion of the skull’s frontal bone, a condition called caries sicca. Caries sicca, a bony finding from gummatous syphilis has been described as “The only reliable and pathognomonic lesion of syphilis…”33 Other findings are of variable reliability.34

Carbon-dating of the skeleton showed it to have lived sometime between 1300 and 1420, corresponding to about a century before Columbus’ first voyage in 1492 to 1493. Three paleopathologists opined on the skeleton number 1216. Charlotte Roberts recognized it as treponemal disease but could not distinguish among them,35 while Rothschild suggested that the population frequency of skeletal involvement was too high for treponemal disease. Secondly, the pattern of disease in the Hull site is classic for yaws. It matches in all details the reports of skeletal findings in yaws and is quite different than those for syphilis. Much of what was diagnosed as disease appeared taphonomic.36 George Armalegos, with extensive experience in viewing New World, pre-Columbian bones allegedly showing changes due to syphilis, was impressed but wanted the confirmation in terms of quantity rather than quality.

Support for the existence of venereal syphilis in pre-Columbian Europe comes from Dr Mattie Hennenberg37 and his wife based on the examination of 300 Greek skeletons buried in a southern Italian port in 600 BCE, with the claim that many of them showed changes similar to those of the Hull friary skeletons, indicative of syphilis; however, taphonomy could be a confounder. The term taphonomy (from the Greek taphos [τάφος] meaning burial and nomos [νόμος] meaning law) was introduced to paleontology in 1940 by Russian scientist Ivan Efremov to describe the study of the transition of remains, parts, or products of organisms from the biosphere to the lithosphere, that is a creation of fossil assemblages.38

Hennenberg, a dental specialist, claimed that the upper central incisor teeth from two skeletons showed “grooves,” proof of congenital syphilis. A second “dig” of old bones from a port near Pompeii offers similar bony findings. Recent research based on exhumed human skeletons from a cemetery at an East London church, St Mary Spital, identified rough patches on skulls and
limbs of some of the skeletons, pointing toward a syphilitic origin for such findings. This study scores over its predecessors in terms of executing radiocarbon dating of the exhumed samples, estimated to be 95% accurate. Brian Connell, an expert from the Museum of London who studied the bones, opined that the skeletons were buried before the Columbus voyage. He said “We’re confident that Christopher Columbus is simply not a feature of the emergence, and timing of the disease in Europe.” Two of the syphilitic skeletons unearthed from the site were from 1200–1250, while the other 5 were from 1250–1400, preceding Columbus’ birth. They were buried with coins and other objects that helped the experts corroborate the radiocarbon dating results.11,39

The Unitarian hypothesis, based on skeletal morphology data,40 has recently been challenged by analysis of the molecular evolution of the tpr C, D, I, K, G, and J genes in the pathogenic genus Treponema.41 The elusive outcome of past research warrants future exploration. The advent of phylogenetic systematic analysis may prove beneficial in exploring the veracity of the findings. It is that field of biology that deals with identifying and understanding the evolutionary relationships among the many different kinds of life on earth, both living (extant) and dead (extinct).

Evolutionary theory states that similarity among individuals or species is attributable to common descent or inheritance from a common ancestor. Thus, the relationships established by phylogenetic systematics often describe a species’ evolutionary history and, hence, its phylogeny, the historical relationships among lineages or organisms or their parts, such as their genes.42 This modality was made use of to analyze the data from 21 genetic regions examined in 26 geographically disparate strains of pathogenic Treponema.43 Of all the strains examined, the venereal syphilis–causing strains originated most recently and were more closely related to yaws-causing strains from South America than to other nonvenereal strains.

Old World yaws–causing strains occupied a basal position on the tree, indicating that they first arose in human history, and a simian strain of Treponema pallidum was found to be indistinguishable from them. These results lend support to the Columbian theory of syphilis’ origin, while suggesting that the nonsexually transmitted subspecies arose earlier in the Old World. In yet another study,44 using an integrative phylogenetic and paleopathologic approach, syphilis seems to have emerged in the time span between 5000 years before present (yBP) and 16,500 yBP, in the Americas, because the resulting evolutionary rate is compatible with those observed in other bacteria; however, these studies relied on 2 bacterial isolates from individuals with alleged yaws from a site where antibiotic treatment of yaws had altered the picture. It is unclear what disease was present in the two isolates on which they based their studies. The suggested time span for origin of syphilis of 5000 to 16,500 yBP is still debatable, especially in view of skeletal evidence supporting origin 2000 to 1800 yBP. In contrast, if the claims of pre-Columbian venereal syphilis outside the Americas are taken into account, the place of origin remains unresolved.

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4 Opdyke DL. Bulnesia sarmientoi. Food Cosmet Toxicol. 1974;12:905

SKInmed. 2012;10:8–12

January/February 2012

COMMENTARY

Origin and Evolution of Syphilis
HISTORICAL DIAGNOSIS & TREATMENT: SYCOSIS (continued from page 7)

SYNONYMS: ACNE SYCOSIS; SYCOSIS BARBAE, SEU MENTI; SYCOSIS NON PARASITICA; MENTAGRA; FOLLICULITIS BARBAE, SEU PILORUM.

Sycosis is a chronic inflammatory disease of hairy parts of the skin characterized by tubercles, papules and pustules, each of which is pierced invariably by the shaft of a hair. In the great majority of cases the disease is limited to the region of the beard in men, though it may occur on the eyebrows, scalp, axillae and pubes. On the face it starts usually as one or more ill defined patches and may remain confined in certain areas or spread so as to include in time the whole bearded region. The disease does not extend to non-hairy parts. Itching is severe.

The disease is feebly contagious and in not infrequently transmitted by the barber shop razor. The pyogenic staphylococci sometimes develop from eczema of the bearded region. Sycosis on the upper lip, which is a favorite location, is often associated with chronic rhinitis. The nasal secretion may be the cause of the sycosis or the sycosis by extension may affect the vibrissae and cause the Schneiderian membrane to become swollen and exquisitely sensitive. Sycosis sometimes develops from eczema of the bearded region. The disease is feebly contagious and in not infrequently transmitted by the barber shop razor. The pyogenic staphylococci are invariably present in the pus.

DIAGNOSIS: Numerous pustules pierced by hairs are almost pathognomonic of the disease. Trichophytosis barbae begins as a scaling spot and later produces a lumpy condition of the skin; from every node many hairs project and these may be twisted, split or broken. The spores are easily found with the microscope. In pustular eczema the pustules are not so accurately located about the hairs, the crusting is greater and the crusts cover raw, oozing surfaces. The disease spreads readily to non-hairy parts. Itching is severe.

TREATMENT: Epilation is the most essential part of the treatment. Each day all the hairs in a given area of the affected region should be extracted. Pasta zinci Lassar, N. F., is to be applied plentifully and kept as constantly as possible in close contact with the skin. In very obstinate cases with thickening of the skin the amount of salicylic acid may be increased to 10-15 per cent. Exposures to the X-rays carried to the point of producing a slight erythema and falling of the hair, have a brilliant curative effect, but every precaution must be observed not to cause dermatitis actinica.

SKINmed. 2012;10:8–12

COMMENTARY

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We present two patients with kerions who are representative of more than 3 dozen similar patients seen in more than 2 decades of observation in our clinic. Recognizing that kerions are delayed-type hypersensitivity (DTH) reactions,1 we treated all our patients with short courses of anti-inflammatory agents, and all had resolution of their lesions.

CASE 1
Patient 1 was a 7-year-old African American boy who was taking oral cephalaxin for a cultured methicillin-sensitive *Staphylococcus aureus* markedly crusted, boggy, alopecic tumefaction on the left lateral scalp that was associated with markedly enlarged postauricular and posterior cervical nodes. He had taken the antibiotic for 2 weeks without any resolution. A fungal culture obtained from a scaling scalp site distant from the kerion was positive for *Trichophyton tonsurans*, and the diagnosis was kerion. He was treated with two drops (94 mg) of saturated solution of potassium iodide (SSKI) three times daily2,3 and 2.5% selenium shampoo twice weekly.4 Two weeks later, the crusting, swelling, and adenopathy had resolved, and 2 months later the hair had regrown without scarring.

CASE 2
Patient 2 was a 9-year-old African American boy who had been treated with adequate doses of griseofulvin for 4 weeks for a crusted, nodular, alopecic plaque on the posterior scalp (Figure 1) along with a markedly enlarged posterior cervical node. Bacterial and fungal cultures were negative. The clinical diagnosis was kerion, and treatment with prednisolone 1 mg/kg/d and selenium sulfide shampoo was instituted. Three weeks later, the plaque had cleared and new hair started to regrow (Figure 2). Within 2 months, the hair had completely regrown without scarring.

DISCUSSION
Kerion formation is the inflammatory extreme of tinea capitis, producing a large, painful, crusted plaque on the scalp, often with purulent discharge and cervical lymphadenopathy. Kerions are the result of a massive DTH reaction to a dermatophyte.1 Positive DTH skin tests, lesional histopathology, and immunofluorescence studies are all consistent with this concept,1,5,6 proposed originally by Birt and Wilt7 in 1954 and later supported by Rasmussen and Ahmed.8 Inasmuch as the kerion is an immunologic event, this helps explain why antibiotics, whether antibacterial or antifungal, are ineffective (in spite of positive cultures) and why all our patients responded to anti-inflammatory treatment with complete resolution of the kerions and subsequent regrowth of hair.

Treatment of kerions has been directed primarily toward the underlying dermatophyte, often with protracted courses of griseofulvin; however, we believe the inflammation, rather than the infection, should be the initial focus of kerion treatment. The clinical findings and treatment outcomes for our two patients with kerion treated with short courses of anti-inflammatory agents are representative and exactly similar to the other patients with kerion seen in our clinic.

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In patients treated prior to 2001, we saw complete resolution in kerions treated with SSKI in 22 of 25 patients within 2 to 4 weeks. This is similar to the resolution of kerions alluded to by Dobson and was also similar to the resolution routinely seen in sporotrichosis. The three patients who did not respond to SSKI (2 did not take it due to the taste, and 1 had worsening of his “id” reaction) had rapid clearance on prednisolone. After 2001, when SSKI became scarce because of the threat of nuclear attacks and dirty bombs, we shifted to prednisolone and noted complete response to treatment in 15 of 15 patients. With both treatment protocols, the kerions cleared and the patients’ hair subsequently regrew without scarring.

Two prospective randomized, controlled studies by other investigators have examined the treatment of kerions with oral doses of corticosteroids. Neither demonstrated a difference in the management of kerion between using oral corticosteroids plus griseofulvin vs griseofulvin alone. These findings are contrary to our observations that all our patients responded to short courses of anti-inflammatory agents and are also contrary to oral corticosteroids being recommended for kerions that present simultaneously with “id” eruptions, as well as in situations in which the kerion becomes “inflamed.” In addition, John Kenney (personal communication, 1983), who treated this disease in many children, routinely included oral corticoids in his regimen for kerions and saw results similar to ours.

We believe untreated kerions require 3 to 6 months to resolve. Many case reports consistent with this concept have been published. In one of our patients, who preferred not to take prednisolone and was treated with griseofulvin alone, the kerion took 4 months to resolve. In contrast, patients treated with anti-inflammatory treatment responded rapidly.

**CONCLUSIONS**

Based on our observations, we believe the addition of prednisolone to the treatment of kerions is safe and allows the duration of therapy to be dramatically shortened. Adjunctive therapy with selenium sulfide shampooing remains useful, and griseofulvin may be continued if scaling from tinea capitis remains after the kerion resolves. Further studies would help resolve the differences in the prospective trials compared with the clinical observations.
REFERENCES


The power to calm inflammatory acne

- Inflammation is an important aspect in the pathophysiology of acne.
- Both laboratory and clinical studies document the anti-inflammatory effects of minocycline.

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Important Information

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Pityriasis rubra pilaris (PRP) comprises a group of chronic disorders that demonstrate circumscribed follicular keratosis with palmoplantar keratoderma. Both familial and acquired forms have been recognized. The former is infrequent and usually occurs in childhood. The bimodal or trimodal distribution usually involves a peak case incidence in the first and second decades of life, and it affects both men and women. Its etiology and management has remained a challenge. Occasionally, PRP is associated with other diseases, and it was speculated that the disorder might be the result of an abnormal immune response to some antigenic stimuli. Familial occurrence of the disease might point to genes that predispose the individual to develop the disorder after certain precipitating events. The occurrence of PRP in patients with the human immunodeficiency virus (HIV)/AIDS is a topic of recent debate.

**CLINICAL CRITERIA/CLASSIFICATION**

Pityriasis rubra pilaris is an uncommon inflammatory dermatosis that is well recognized across the globe. Erythroderma is a common presentation. A precise diagnosis of pityriasis rubra pilaris is based on morphologic features and is classified into 6 types: classic adult onset (type I), atypical adult (type II), classic juvenile (type III), circumscribed juvenile (type IV), atypical juvenile (type V), and human immunodeficiency virus–associated (type VI). Several conventional systemic and/or topical treatments are currently in use. Largely, their results are unsatisfactory and limited by long-term toxicity. The authors investigate the efficacy of a wide spectrum of drugs by examining historical (archive) and promising (modern) treatment modalities for the treatment of pityriasis rubra pilaris. *(SKINmed. 2012;10:18–23)*

**CHALLENGES AND PROMISING TREATMENTS**

Historically (Archive) Important Modalities

The diagnosis and treatment of PRP have always been a source of great interest. At present, there is no acclaimed treatment
PROMISING (MODERN) MODALITIES

The advent of synthetic retinoids has brought about a revolution in the therapy for PRP, especially in recalcitrant cases. Isotretinoin at a dosage of 1 mg/kg/d to 2.2 mg/kg/d for 12 to 16 weeks has proven to be beneficial. Ertretinate has also been shown to be effective at a dosage of 0.5 mg/kg/d to 1 mg/kg/d for 3 to 5 months. The duration of remission is variable. The side effects of oral retinoids may warrant the discontinuation of therapy, especially in children.\textsuperscript{15–18} Synergism of vitamins A and E has also been effective in PRP.\textsuperscript{8}

Among the topical therapies, vitamin A, calcipotriol,\textsuperscript{19} and tacalcitol have shown promising results. Phototherapy, particularly narrow-band UV-B with oral retinoids has been successful.\textsuperscript{20,21}

Other treatment modalities include methotrexate,\textsuperscript{22} cyclosporine A,\textsuperscript{23,24} stanozolol,\textsuperscript{25} penicillin, and antitubercular\textsuperscript{19} drugs. HIV/AIDS-associated PRP is recalcitrant to therapy. Highly active triple antiretroviral drug therapy has shown positive results in alleviating symptoms and may cause complete regression in such patients.\textsuperscript{26,27}

Apart from symptomatic and supportive therapy in every case, the use of well-documented medicines is individualized according to physician preference. First-line therapy includes retinoids and/or methotrexate for a few weeks to months until remission is achieved. If the patient does not respond to initial treatment, second-line therapy includes cyclosporine, azathioprine, or antiretroviral therapy. Third-line therapy with calcipotriol, acitretin + narrowband UV-B (TL-01),\textsuperscript{21} acitretin + UV-A-1,\textsuperscript{28} or extracorporeal phototherapy\textsuperscript{29} may be employed under careful supervision.

RETNIOIDS/VITAMIN A DERIVATIVES

Ertretinate\textsuperscript{21} is used in a dose of 0.75 mg/kg to 1 mg/kg daily for up to 4 months. The dose is tapered gradually following adequate response. Isotretinoin, on the other hand, is equally effective in a dosage of 0.48 mg/kg to 3.19 mg/kg daily (mean 1.0 mg/kg + 1.5 mg /kg daily), given over a period of 3 to 6 months. Acitretin has shown satisfactory response in juvenile PRP
patients in a period varying from 1 to 36 weeks. Acitretin can also be combined with phototherapy at a dose of 0.5 mg/kg/d.

**IMMUNOSUPPRESSIVE THERAPY**

Methotrexate has been in use for the past 4 decades in select cases of PRP; however, the response has been variable. Methotrexate and oral retinoids has been tried in patients refractory to oral retinoids alone. Such a combination, however, may cause significant hepatotoxicity. Azathioprine in a dosage of 50 mg to 150 mg daily has been found to be effective in several studies. Cyclosporine, in a dosage of 5 mg/kg/d, has been tried in patients with classic type 1 PRP. The dose is tapered to 1.2 mg/kg/d with adequate response. In addition, cyclosporine has been used effectively to treat a case of juvenile PRP. Topical calcipotriol (vitamin D3) has shown efficacy in PRP without serious side effects except local irritation.

**PHOTOTHERAPY**

Broadband UV-B therapy was unsuccessfully tried in a case of juvenile classic PRP. The same patient, however, responded to narrowband UV-B therapy (TL-01) when combined with acitretin. Acitretin combined with long-wave UV-A (UV-A-1) was successfully used in a case of classic PRP.

Extracorporeal photochemotherapy has also been a source of investigation. Recalcitrant type II chronic adult PRP has also been treated effectively with this therapy. The efficacy of penicillin and antituberculous drugs as possible therapeutic agents for the treatment of PRP was recorded as early as 1965. Recently, a 62-year-old Caucasian woman with progressive erythroderma and type I PRP was treated effectively with a combination of systemic penicillin and vitamin A.

**TOPICAL THERAPY**

Topical pimecrolimus cream 1% was used in a young man with PRP limited to the scalp and face. The lesions cleared with the medication within 2 weeks. Topical tazarotene treatment was recorded to be effective in a 12-year-old Afghani girl with juvenile circumscribed PRP. The medicine led to rapid and sustained remission. Topical vitamin A has been used, and calcipotriol and tacalcitol have shown good results. Emollients and a combination of diluted topical steroids and keratolytics are worth a trial before embarking on any other modality.

In addition, several other therapies, namely vitamin A, cod liver oil, halibut liver oil, adrenocorticotropic hormone + vitamin A, and ascorbic acid in the prescribed dosages, were used in the past to alleviate the symptoms of PRP. The recommended dosages and responses are shown in Table III. These drugs appear to have been replaced in favor of newer drug therapies.

**BIOLOGICS**

Tumor necrosis factor (TNF) blockers as a feasible alternative to PRP therapy continues to show promise since its inception in 2007. TNF is a cytokine involved in the inflammatory process. Cytokines are chemical substances that deliver messages between

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**Table III. Pityriasis Rubra Pilaris: Challenges and Promising Treatment—Historical (Archive) Importance**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year(s)</th>
<th>Recommended Drug(s)</th>
<th>Dosage</th>
<th>Response/Result</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petter¹⁰</td>
<td>1936</td>
<td>Vitamin A</td>
<td>1,000,000 IU/per d × 2 wk</td>
<td>Good</td>
<td>2 patients</td>
</tr>
<tr>
<td>Gunther and Alston²</td>
<td>1973</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayres et al⁸</td>
<td>1979</td>
<td>Vitamins A and E</td>
<td>500,000 IU + 200–4 IU</td>
<td>Synergism of vitamins A and E</td>
<td>1 report</td>
</tr>
<tr>
<td>Skinner et al⁹</td>
<td>1981</td>
<td>Cod liver oil</td>
<td>1–3 mL/d</td>
<td>Worthwhile</td>
<td>Case report</td>
</tr>
<tr>
<td>Brunsting and Sheard¹⁰</td>
<td>1941</td>
<td>Halibut liver oil</td>
<td>1–3 mL/d</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Weiner and Levin¹¹</td>
<td>1943</td>
<td>Carotene</td>
<td>–</td>
<td>Good in some cases</td>
<td>–</td>
</tr>
<tr>
<td>Webster and Falk¹²</td>
<td>1952</td>
<td>ACTH + vitamin A</td>
<td>1,000,000 IU of vitamin A + 10–20 units of adrenocorticotropic hormone/wk</td>
<td>Favorable</td>
<td>2 patients</td>
</tr>
<tr>
<td>Irgang¹³</td>
<td>1968</td>
<td>Ascorbic acid</td>
<td>Oral/intramuscular 500 mg/1 g</td>
<td>Useful in isolated cases</td>
<td>–</td>
</tr>
<tr>
<td>Watt and Jilson¹⁴</td>
<td>1965</td>
<td>Penicillin and antitubercular</td>
<td>Penicillin V 1 g/d + usual antitubercular medication</td>
<td>Equivocal</td>
<td>6 patients</td>
</tr>
</tbody>
</table>

Abbreviations: ACTH, adrenocorticotropic hormone; IU, international unit.
### Table IV. Pityriasis Rubra Pilaris (PRP): Challenges and Promising Treatment—Modern Modalities

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Recommended Drug(s)</th>
<th>Dosage</th>
<th>Response/Result</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hofer et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>1999</td>
<td>Extracorporeal photochemistry</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anderson&lt;sup&gt;30&lt;/sup&gt;</td>
<td>1966</td>
<td>Methotrexate</td>
<td>5–30 mg/wk</td>
<td>Equivocal good</td>
<td>–</td>
</tr>
<tr>
<td>Hunter and Forbes&lt;sup&gt;31&lt;/sup&gt;</td>
<td>1972</td>
<td>Azathioprine</td>
<td>50–200 mg/d</td>
<td>Good</td>
<td>Review</td>
</tr>
<tr>
<td>Usuki et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>2000</td>
<td>Cyclosporine</td>
<td>&lt;5 mg/kg/d</td>
<td>Good in recalcitrant PRP</td>
<td>Case report</td>
</tr>
<tr>
<td>Lim and Tham&lt;sup&gt;39&lt;/sup&gt;</td>
<td>1991</td>
<td>Systemic prednisolone</td>
<td>20–60 mg/kg</td>
<td>Useful in some cases</td>
<td>4 patients</td>
</tr>
<tr>
<td>Brice and Spencer&lt;sup&gt;35&lt;/sup&gt;</td>
<td>1985</td>
<td>Stanozolol</td>
<td>2 mg/d</td>
<td>Good result in some cases</td>
<td>Case report</td>
</tr>
<tr>
<td>Van de Kerkhof and Steijlen&lt;sup&gt;39&lt;/sup&gt;</td>
<td>1991</td>
<td>Calcipotriol</td>
<td>Topical ointment daily</td>
<td>Good in localized case</td>
<td>Case report</td>
</tr>
<tr>
<td>Herbst et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>2000</td>
<td>Retinoid + UV light</td>
<td>Acitretin + UV-A-1 (0.5 mg/k/d)</td>
<td>Good result</td>
<td>Case report</td>
</tr>
<tr>
<td>Kirby and Watson&lt;sup&gt;31&lt;/sup&gt;</td>
<td>2000</td>
<td>Acitretin and narrowband UV-B</td>
<td>Acitretin 0.5 mg/kg/d</td>
<td>Effective</td>
<td>–</td>
</tr>
<tr>
<td>Coras Vogt et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>2005</td>
<td>Fumaric acid</td>
<td>–</td>
<td>Useful</td>
<td>–</td>
</tr>
<tr>
<td>Haenssle et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>2004</td>
<td>Extracorporeal photochemistry</td>
<td>2 J/cm²/1 mo on 2 consecutive days</td>
<td>Good result in isolated cases</td>
<td>–</td>
</tr>
<tr>
<td>Davis et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>2007</td>
<td>Acitretin and etanercept</td>
<td>–</td>
<td>Clinical improvement</td>
<td>–</td>
</tr>
<tr>
<td>Kerr and Ferguson&lt;sup&gt;48&lt;/sup&gt;</td>
<td>2007</td>
<td>Intravenous immunoglobulin</td>
<td>–</td>
<td>Very effective</td>
<td>–</td>
</tr>
<tr>
<td>Gregoriou et al&lt;sup&gt;36&lt;/sup&gt;</td>
<td>2007</td>
<td>Pimecrolimus cream</td>
<td>1% cream</td>
<td>Cleared completely</td>
<td>Case report</td>
</tr>
<tr>
<td>Ruiz-Genao et al&lt;sup&gt;39&lt;/sup&gt;</td>
<td>2007</td>
<td>Infliximab</td>
<td>–</td>
<td>Successful</td>
<td>–</td>
</tr>
<tr>
<td>Muller et al&lt;sup&gt;41&lt;/sup&gt;</td>
<td>2008</td>
<td>Infliximab</td>
<td>–</td>
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<td>Ruzzetti et al&lt;sup&gt;44&lt;/sup&gt;</td>
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<td>Infliximab</td>
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<td>Cox et al&lt;sup&gt;30&lt;/sup&gt;</td>
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<td>Seckin et al&lt;sup&gt;41&lt;/sup&gt;</td>
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<td>Karimian-Teherani et al&lt;sup&gt;37&lt;/sup&gt;</td>
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<td>Topical tazarotene</td>
<td>–</td>
<td>Effective</td>
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<td>Barth et al&lt;sup&gt;42&lt;/sup&gt;</td>
<td>2009</td>
<td>Infliximab and methotrexate</td>
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<td>2009</td>
<td>Adalimumab</td>
<td>Adalimumab&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Vergilis-Kalner et al&lt;sup&gt;20&lt;/sup&gt;</td>
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<td>Narrowband UV-B</td>
<td>–</td>
<td>Cleared in 4 months</td>
<td>Case report</td>
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<sup>a</sup> Continued »
cells in the body. Accordingly, TNF drugs target the effects of TNF-α. The fusion protein, etanercept, recombinant monoclonal antibodies, infliximab and adalimumab, are currently available for use as a therapeutic modality for PRP. In addition, intravenous immunoglobulin has been successfully used in type II adult-onset PRP.

A combination of infliximab and methotrexate proved to be beneficial in a 65-year-old woman with erythroderma due to PRP, after she failed to respond to intravenous methotrexate. Similarly, type III PRP has been treated successfully with this drug. Etanercept has also been tried with success both in juvenile and adult-onset PRP. Adalimumab treatment of PRP caused a rapid and sustained remission of the disease.

Recently, TNF-α antagonists (infliximab and etanercept) were used in 7 patients with adult-onset PRP who were resistant or ineligible for conventional systemic treatment. Follow-up was performed after complete remission and treatment discontinuation. Six patients obtained complete remission after a single course of anti-TNF-α therapy; mean therapy duration was 19.3 weeks (range, 6 to 48 weeks). All patients obtained significant clearing, with improvement in ≥75% of body surface area at week 12. Only a single patient had disease relapse at the follow-up period of 12 months. The information on biologics as a treatment modality in PRP is outlined in Table IV.

**FIVE-YEAR VIEW**

Since the first reported case of the disease, PRP has remained a consistently recorded and researched entity. Its etiology and management has always been a challenge. It is seen in adults as well as children. Occasionally, PRP may be associated with other diseases, and it is speculated that the disorder may be the result of an abnormal immune response to antigenic stimulation.

Familial occurrence of the disease might point to genes that predispose the individual to develop the disorder after certain precipitating events. The occurrence of the disease in patients with HIV/AIDS has sparked debate as to whether it is yet another variant of PRP. Several distinctive features recognize the entity.

Conventional systemic and/or topical treatments are prevalent. Largely, their response is unsatisfactory and limited by long-term toxicity.

Consequently, emerging treatments warrant effort to bring into light the newer promising (modern) drugs in the background of historical (archive) ones. Indeed, it is necessary to enlighten physicians about the turnover of drugs for PRP in order to evolve a viable and acceptable therapy for its treatment. The advent of TNF blockers has been hailed as a major breakthrough. Accordingly, literature scanned through a Medline search has revealed 16 outstanding contributions in the past 5 years. Infliximab, etanercept, and adalimumab are some of the fascinating drugs that need to be looked into judiciously in terms of dosages, duration, and long-term follow-up for PRP.

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A critical question in the treatment of chronic wounds is whether and when debridement is needed. The three most common chronic wounds are the diabetic foot ulcer (DFU), the venous leg ulcer, and the pressure or decubitus ulcer. Surgical debridement, aimed at removing necrotic, devitalized wound bed and wound edge tissue that inhibits healing, is a longstanding standard of care for the treatment of chronic, nonhealing wounds. Debridement encourages healing by converting a chronic nonhealing wound environment into a more responsive acute healing environment. While the rationale for debridement seems logical, the evidence to support its use in enhancing healing is scarce. Currently, there is more evidence in the literature for debridement for DFUs than for venous ulcers and pressure ulcers; however, the studies on which clinicians have based their rationale for debridement in DFUs possess methodologic flaws, small sample sizes, and bias. Thus, further studies are needed to develop clinical evidence for its inclusion in treatment protocols for chronic wounds.

Here, the authors review the scientific evidence for debridement of DFUs, the rationale for debridement of DFUs, and the insufficient data supporting debridement for venous ulcers and pressure ulcers. (SKINmed. 2012;10:24–26)
SCIENTIFIC EVIDENCE FOR DFU DEBRIDEMENT

The biological and molecular basis for debridement has been investigated in several studies.10,11 Molecular and histologic analyses of biopsies from the nonhealing edge of a chronic wound have been suggested to validate the use of debridement.10

Keratinocytes become activated following wounding and are key players in restoring the epidermal barrier during wound healing.12 Keratinocytes and fibroblasts at the nonhealing edges of chronic wounds were shown to exhibit not only a pathogenic phenotype detrimental to healing but also a slowed migratory capacity.10–13 In chronic wounds, the keratinocytes multiply at a higher rate than usual (hyperproliferation), yet they are unable to migrate into the wound as would be normally expected.10–12 Basically, keratinocytes on a chronic wound edge are capable of proliferating but are unable to migrate properly.12 These nonhealing keratinocytes of the chronic wound edge are marked by induction of c-Myc and nuclearization of β-catenin, which may contribute to the inhibition of migration.10–12 Many clinicians visually identify this nonhealing phenotype as a “callus,” indicating the need for removal to facilitate wound healing.14 Debridement seems to be a reasonable solution to the problem of nonmigratory tissue in the margins of chronic wounds. Researchers suggest that debridement will be effective if unresponsive cells are surgically removed, and cells responsive to wound healing signals and topical agents are optimized.11

RATIONALE FOR DEBRIDEMENT OF DFUs

The benefits of debridement include removal of bacteria, senescent cells, and hyperproliferative nonmigratory tissue and stimulation of growth factor activity.13

Bacterial burden in a wound likely impedes healing,16 as greater bacterial load and certain types of bacteria have been shown to reduce healing responses.17,18 Bacteria in chronic wounds stimulate a prolonged inflammatory response with a concomitant release of free oxygen radicals and various lytic enzymes, ultimately causing tissue damage.19 In addition, biofilms, which are communities of bacteria and other organisms embedded in an extrapoly saccharide matrix within the wound bed, show increased resistance to antimicrobial agents and to the host immune system.20,21 Debridement is an effective way to remove bacterial burden and biofilms from nonhealing wounds.

Additionally, growth factors are reduced in chronic wounds, including platelet-derived growth factor, fibroblast growth factor, epidermal growth factor, and transforming growth factor β.22 Dead tissue within chronic wounds, which is removed by surgical debridement, is unresponsive to growth factors.23 In addition, the bleeding and platelet activation caused by debridement stimulates the production of blood-borne growth factors, further promoting wound healing.24

Senescent cells have markedly decreased proliferation and protein production.17 Chronic wound fibroblasts are less receptive to growth factor stimuli,25 making these wounds less likely to heal or respond to treatments.16 Overall, debridement removes both the hyperproliferative edge and the senescent cells of the chronic wound, thus allowing the remaining cells to undergo normal proliferation, migration, response to treatment, and healing.

DEBRIDEMENT AND VENOUS ULCERS

Another example of a chronic wound is venous ulcer. Venous insufficiency is the most common cause of lower-extremity ulcers and accounts for the development of approximately 1 million venous ulcers in patients in the United States with venous insufficiency.27 There are many theories for the mechanism of venous ulcer development, including pericapillary fibrin cuff deposition, abnormalities of the fibrinolytic system, trapping of growth factors by macromolecules in the dermis, and leukocyte plugging in the vessels of the lower extremities.28–30 The treatment modalities for venous ulcers include bed rest with leg elevation31; compression therapy32; aspirin33; pentoxifylline34; skin grafting,35 including cultured epidermal autografts and allografts,36,37 superficial venous surgery38; and debridement.17,39

The data supporting debridement for venous ulcers are even more sparse than for DFUs. The role of debridement in the treatment of venous ulcers has not been proven, although it is used as a standard of care.39 One controlled, prospective cohort study involving 53 patients for 12 months evaluated sharp debridement in combination with standard treatment regimens for nonhealing venous leg ulcers.40 The study group contained ulcers that had slough, nonviable tissue and no granulation tissue, while the control group had ulcers with 15% to 20% granulation tissue without slough or nonviable tissue. Although they failed to reach statistical significance, the authors concluded that sharp debridement was effective at initiating the healing process. They found a 6-cm² reduction in the mean surface area of the study group ulcers, compared with a 1-cm² reduction in the control group in the first 4 weeks (P = .02).40

Clinical experience also dictates that venous ulcers are commonly more difficult to debride than most DFUs, and it is more time-consuming for the clinician to achieve viable tissue margins in these cases; therefore, chronic venous ulcers, much like DFUs, are in need of evidence-based standardized treatment plans.

DEBRIDEMENT AND PRESSURE ULCERS

The most common cause of chronic wounds is the pressure ulcer. While the rationale for debridement is excellent as part of standard care when treating pressure ulcers, given the multiple comorbidities coexistent in patients with pressure ulcers, the data supporting debridement for pressure ulcers are the least substantial of the 3 common chronic wounds.
CONCLUSIONS

Surgical debridement, despite the need for better data, is part of standard care in the treatment of chronic, nonhealing wounds, with better evidence for DFUs than for venous ulcers. Some may be concerned that debridement may create a new portal of entry for bacterial organisms, but studies have shown that the rate of infection does not increase in debrided wounds. Debridement is for bacterial organisms, but studies have shown that the rate of infection does not increase in debrided wounds. Debridement is for bacterial organisms, but studies have shown that the rate of infection does not increase in debrided wounds. Debridement is for bacterial organisms, but studies have shown that the rate of infection does not increase in debrided wounds.46 Debridement is for bacterial organisms, but studies have shown that the rate of infection does not increase in debrided wounds. Debridement is for bacterial organisms, but studies have shown that the rate of infection does not increase in debrided wounds.

REFERENCES

Cutaneous Tuberculosis: A Diagnostic Dilemma

Virendra N. Sehgal, MD;1 Prashant Verma, MD;2 Sambit N. Bhattacharya, MD;2 Sonal Sharma, MD;3 Navjeevan Singh, MD;3 Nishant Verma, MD4

Cutaneous tuberculosis continues to be one of the most difficult conditions to diagnose. It is a challenge particularly in developing countries due to the lack of resources. The authors define the classification and clinical manifestations considered predictive of its diagnosis.

Tuberculosis (TB) is a common disease worldwide,1 and its clinical incidence has been impacted by the emergence of the human immunodeficiency virus (HIV), increased transmigration from endemic countries, and its transmission in health care facilities, prisons, homeless shelters, and other crowded settings.2–5 TB is largely an airborne infection; however, skin manifestations may be caused by hematogenous spread or the contiguity from latent and/or active foci of infection. Primary inoculation, although uncommon, is another known mode of transmission. HIV infection, intravenous drug abuse, diabetes mellitus, immunosuppressive therapy, malignancies, end-stage renal disease, and infancy may predispose to TB. Although cutaneous TB (CTB) is a well-recognized clinical entity, it often poses a diagnostic dilemma for physicians;6 therefore, it is important to perform a careful review of clinical presentations in each patient, which may prove predictive of its diagnosis.7,8

CLASSIFICATION

The most widely accepted CTB classification is based on the route of infection.6,9 Exogenous inoculation occurs after the direct inoculation of Mycobacterium tuberculosis into the skin of a person who is susceptible to infection (vide infra). This may cause TB verrucosa cutis (TBVC), TB chancre, and some cases of lupus vulgaris (LV), whereas endogenous infection is caused by either lymphatic or hematogenous spread or a contiguous extension. Occasionally, lymphatic spread is seen in LV. Hematogenous spread, on the other hand, is responsible for acute miliary TB, metastatic tubercular abscess, gummatous TB, papulonecrotic tuberculid (PNT), and lupus vulgaris. Contiguous extension from the underlying lesion is a characteristic feature of both scrofuloderma and TB cutis orificialis (TBCO).

In attempt to embellish the preceding classification, it has been divided into multibacillary and paucibacillary variants based on the bacterial load. The former is recognized by the characteristic morphology of the organism in the tissue sections stained with Ziehl-Neelsen method, complemented by in vitro recovery of M tuberculosis, while sparse bacilli on histological examination and rare in vitro culture isolation2 identify the latter. Unfortunately, it is difficult to distinguish the organisms in paucibacillary TB.

CLINICAL FEATURES

Although the prevalence of CTB accounts for 1.5% of all cases of TB, it is, nevertheless, important to consider the entity when patients present with a suggestive clinical morphology. CTB has many forms, including multibacillary and paucibacillary CTB, which are defined in detail below.

MULTIBACILLARY CTB

TB chancre/inoculation TB

Tuberculous chancre (primary inoculation TB) is a variant of multibacillary CTB that results from direct introduction of mycobacteria into the skin or mucosa of an individual who neither had tubercular infection in the past nor was immunized with Bacille Calmette-Guérin (BCG). Trauma also facilitates the entry of the organism into the skin.10,11 Face and other exposed areas are vulnerable sites of introduction. The organism multiplies in tissue macrophages and migrates to
regional lymph nodes. An inflammatory papule develops in 2 to 4 weeks after inoculation that breaks down into a firm, non-healing, shallow, nontender, undermined ulcer with a granulomatous base. Painless regional lymphadenopathy is a cardinal sign, appearing after about 3 to 8 weeks. Numerous bacilli are demonstrable at the inoculation site and regional lymph node. The ultimate ulceroglandular lesion is a “mirror image” of the Ghon’s complex. Its clinical course varies according to the host-immune response.12

The primary lesion heals with scarring after 1 to 3 months; however, with a less effective host-immune response, the bacterial load remains high, and healing may be delayed up to 12 months. Regional nodes may suppurate, erode, and perforate the surface of overlying skin, resulting in scrofuloderma. Latent foci of infection may persist at the site and progress to either LV or TBVC despite evident tuberculin sensitivity. Hematogenous dissemination of mycobacteria from skin can result in TB at other sites, particularly bones or joints, or progress to acute miliary disease with poor outcome.

SCROFULODERMA (TB COLLIQUATIVE CUTIS)
Scrofuloderma (TB colliquative cutis) is the most common form of CTB in children. It results from the direct extension from an underlying TB focus, such as a regional lymph node or infected bone or joint, to the overlying skin. Lesions present as firm, painless, subcutaneous, red-brown nodules overlying an infected focus, which gradually enlarge and suppurate, forming ulcers and sinus tracts that drain watery, purulent, and/or caseous material. The ulcers heal with typical puckered scarring.13

TB CUTIS ORIFICIALIS
The lesions associated with TBCO are frequently characterized by erythematous, edematous nodules, and/or plaques. Painful central ulceration covered by necrotic pseudomembranous material with an irregular border is apparent. Constitutional symptoms of TBCO include fever, malaise, weight loss, and night sweats. The oral mucosa and tongue are the most commonly afflicted sites.2 The exact mechanism resulting in TBCO is unknown; however, ingestion of bacilli in sputum from active pulmonary TB, hematogenous and lymphatic spread, and direct spread from adjacent organs has been alleged.14 with ingestion of bacilli in sputum being the most accepted mode.15 There has been a reported case of isolated perianal TB without pulmonary or gastrointestinal involvement.16

DISSEMINATED MILIARY TB
Disseminated miliary TB is characterized by a wide dissemination of M tuberculosis in the body and shows a distinctive pattern of millet-sized, multiple, tiny lesions on chest x-ray, distributed throughout the lung fields. It may hematogenously infect any number of organs including the lungs, liver, and spleen in patients with advanced TB. There is a systemic failure of the cell-mediated immune system that allows and facilitates the spread of infection, resulting in rapid deterioration and death.4,17,18 Certain events, infections, and medications that suppress the body’s cell-mediated immune system may precipitate this infection. Although miliary TB is rare and well known for its occurrence in children, it is an increasingly serious infection in immunosuppressed patients, such as those infected with HIV and those on long-term oral corticosteroid therapy or other immunosuppressive therapies for organ transplant or inflammatory and autoimmune conditions.

Cutaneous skin lesions associated with miliary TB consist of small, erythematous to violaceous papules or pustules with hemorrhagic necrosis and umbilication affecting a substantial portion of the body. Healing is indicated by the presence of atrophic, depressed scars surrounded by a brownish, hyperpigmented halo.

METASTATIC TUBERCULOUS ABSCESES (GUMMA)
Metastatic tuberculous abscesses (gumma) may either arise from the breakdown of an old healed tubercle that still has live organisms or in immunocompromised individuals.2,4 Accordingly, it is usually seen in malnourished children and immunosuppressed adults.6 Single or multiple, nontender, fluctuant nodules develop, forming draining sinuses and abscesses (Figure 1). Nodules may occur at any location without specific predominance.

![Figure 1. Metastatic tuberculous abscesses (gumma): a single, nontender, fluctuant nodule, draining sinus is apparent.](image-url)
PAUCIBACILLARY CTB

**TB Verrucosa Cutis**

TBVC occurs after direct inoculation of *M. tuberculosis* into the skin of previously infected individuals. It manifests as a painless, solitary, purplish or brownish red warty plaque that may extend peripherally, causing central atrophy, or form fissures that exude pus or keratinous material (Figure 2). It is often accompanied by lymphadenopathy. Skin lesions may evolve and persist for years, although spontaneous resolution may also occur. Response to treatment is favorable.6,19

**LUPUS VULGARIS**

LV is a chronic and progressive form of CTB that is widely described as the most common form. Lesions occur on normal skin as a result of direct extension from underlying deeper TB focus, by lymphatic or hematogenous spread, after primary inoculation or BCG vaccination, or in scars of old scrofuloderma.20 Lesions are typically small, solitary, nodular, sharply defined, and reddish brown with a gelatinous consistency. “Apple-jelly” nodules present on the head and neck of individuals in Western countries, while lesions on the lower extremities or buttocks are present in individuals in tropical and subtropical areas. It has several clinical variations such as classic plaque or keratotic hypertrophic, ulcerative, and vegetating. The plaque type begins as discrete, red-brown papules that coalesce and form plaques with a slightly elevated verrucous border and central atrophy (Figure 3). Persistent lesions may damage underlying tissue and ulcerate, causing severe disfigurement and an increased risk of skin cancer.21

**TUBERCULIDS**

The relationship between tuberculids and TB is a subject of continuing debate. They are generalized exanthems with a moderate to high degree of host immunity to TB. Patients are usually in good health and show (1) positive tuberculin skin test results; (2) inactive tuberculous involvement of viscera or lymph nodes; (3) negative staining and culture for pathogenic mycobacteria in affected tissue; and (4) skin lesions that heal with remission or treatment of TB. Its morphological variations include lichen scrofulosorum (LS),22 erythema induratum of Bazin (EIB), and PNT.

Tuberculids may be classified into 2 groups: (1) true tuberculids, and (2) facultative tuberculids. *M. tuberculosis* plays a major etiologic role in the former, while it is one of several possible etiologic agents in the latter. Tuberculids were once believed to be a result of hypersensitivity to the presence of mycobacterial antigens within a host of previously acquired immunity to TB; however, most are now known not to be uniquely caused by *M. tuberculosis*. PNT and LS are still widely accepted as true tuberculids and EIB as a facultative tuberculid.22
LICHEN SCROFULOSORUM
LS is an eruption of multiple, small, grouped, asymptomatic, firm, perifollicular, lichenoid papules and/or plaques (Figure 4), most often affecting children or young adults, that progresses and subsides within weeks to months without scarring. An association between LV, caries of the spine, LS, and its unusual occurrence in pulmonary TB has been described in the past.

ERYTHEMA INDURATUM OF BAZIN
EIB is a TB-associated panniculitis that presents with multiple, painful, recurring, ulcerated nodules that affect the legs of women. Pre-existing vascular disease may predispose patients to lesions during exposure to cold weather. Lesions are chronic, slow to resolve (if at all), and result in atrophic hyperpigmented scarring after several months (Figure 5). Although patients show TB skin hypersensitivity, acid-fast bacilli (AFB) are rarely identified. A study from Spain demonstrated that about 10% of cases were positive for *M. tuberculosis* using polymerase chain reaction (PCR). A case series and literature review revealed that organisms, such as *Mycobacterium bovis* and *Mycobacterium marinum*, may also be involved in the etiology of EIB, although no evidence of such was found during the investigation. It was suggested that EIB has diverse etiologies with varying pathogenesis, leading to similar histological changes, and the cases analyzed may not have had an infectious etiology (suggesting a facultative tuberculid picture).

PAPULONECROTIC TUBERCULID
Papulonecrotic tuberculid occurs as a chronic and recurrent symmetric eruption of necrotizing skin papules appearing in clusters and healing with varioliform scars (Figure 6). Tubercle bacilli are difficult to demonstrate, but patients typically have an internal focus of TB and are tuberculin sensitive, and skin lesions resolve after anti-TB therapy. TB DNA has been detected in these lesions using PCR amplification reactions. Lesions appear on the exterior aspects of extremities, knees, elbows, buttocks, and lower trunk in a symmetric distribution, often in clusters. Individual lesions are asymptomatic, small, dusky red papules with a central punctum or crust. Involution is common after 6 to 8 weeks.

DIAGNOSIS
Diagnosis of CTB is based on relative and absolute criteria, in addition to supportive immunologic evidence.
RELATIVE DIAGNOSIS

CARDINAL MORPHOLOGIC FEATURES (vide supra)
A characteristic history of evolution of the disease is distinct in re-infection and re-activation. In re-infection, a history of primary infection or BCG vaccination must be obtained. The latter forms an important component of the immunization program in some countries, including India, and may be identified by a BCG vaccination scar at the insertion point on the left deltoid. In re-activation, on the other hand, a history of TB, established by clinical and/or investigative procedures, followed by cure and an asymptomatic period on completion of specific anti-tubercular therapy. Often, the only evidence of past infection may be pulmonary scarring and calcification visible on radiography. Subsequently, any event that lowers the cell-mediated immunity may re-activate the condition, resulting in its relapse.

MANTOUX TEST
A positive Mantoux test indicates the cell-mediated skin hypersensitivity to tuberculin. The response in re-infection may be higher as compared with that in re-activation TB. This in vivo test correlates well with the migratory index of lymphocytes to tuberculin antigen, assayed through leukocyte migration inhibition test. A strongly positive reaction, however, indicates active TB. It has only a limited diagnostic application in countries where the infection is highly prevalent and BCG forms an integral part of the immunization program and the majority of adults are tuberculin positive; nevertheless, it may be a useful adjunct in developed countries.

Microscopic examination of the tissue section may depict a tuberculoid and tuberculous granuloma. The former, characterized by a focal accumulation of epithelioid cells, a few giant cells, and surrounding mantle of mononuclear cells, is a relative parameter encountered in LV and TBVC. It also demonstrates caseation necrosis in the center. It may be possible to demonstrate AFB on Fite's stain. This granuloma fulfills an absolute criterion for diagnosis of TB and typifies scrofuloderma.

ABSOLUTE DIAGNOSIS
An absolute diagnosis consists in the demonstration of AFB on Ziehl-Neelsen's staining of the smear, prepared from material from lesions. The colonies should be further subjected to biochemical and pigment production tests to confirm M tuberculosis. Recovery of M tuberculosis on inoculation of material from lesions into guinea pigs.

In an effort to achieve universal access to high-quality diagnosis and ultimate patient-centered treatment as envisaged by World Health Organization (WHO), it is important to be aware of the diagnostic modalities thus far available in the global arena.

NONTUBERCULOUS MYCOBACTERIA
Physicians should be aware of nontuberculous mycobacteria (NTMB) in the current context, because they are environmental organisms capable of causing chronic disease in humans worldwide. The prevalence of NTMB disease is steadily increasing and has emerged in previously unrecognized populations. They, too, are a diagnostic challenge. TB verrucosa cutis–like lesions may be caused by M bovis.

ATYPICAL MYCOBACTERIOSIS
Mycobacterium avium-intracellulare (MAI) is now a well-established cause of cervical lymphadenitis, simulating scrofuloderma, especially in the pediatric age group in the developed world. In addition, LV-like morphology may also be encountered following primary MAI infection.

HIV INFECTION AND CTB
HIV-infected patients are vulnerable to contract TB. TB may present as a rapidly progressive disease in immunosuppressed patients. Miliary TB is common and may be associated with cutaneous manifestations. Disseminated CTB may show a high yield of mycobacterium from an unusual dermatitis in this group. Despite the dissemination of the organism, the diagnosis of TB may be difficult. In addition, atypical presentations of oesophago-pleuro-cutaneous and pleuro-cutaneous fistula may be seen. In addition to the decrease in tuberculin reactivity, atypical chest radiographic patterns are common. Biopsy and aspirates of peripheral and regional lymph nodes, liver, and bone marrow provide the highest yield and are used for early diagnosis.

Co-lesional acquired immunodeficiency syndrome–associated cutaneous Kaposi's sarcoma and M tuberculosis–associated granulomatous inflammation have recently been documented. Tuberculous gumma, new-onset cervical lymphadenopathy, and worsening of the pre-existing lymphadenitis, yet another high-risk immune reconstitution inflammatory syndrome, has previously been described.

CONCLUSIONS
Reviewing the prevalence and variations in the clinical expression of CTB across the globe may assist in evolving a uniform pattern of the disease vital for a core curriculum. The comprehension of the text is, therefore, crucial in developing treatment strategy through the recommendations of WHO. WHO believes that the same treatment regimen for pulmonary and/or extrapulmonary TB should be used.
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SELF-TEST REVIEW QUESTIONS

W. Clark Lambert, MD, PhD, Section Editor

Instructions: For each of the following numbered questions, choose the most appropriate lettered response(s) Unless directed to choose only one lettered response, all, some, or none of the responses may be correct.

1) Exogenous inoculation, due to the direct inoculation of *Mycobacterium tuberculosis* into the skin of a person who is susceptible to infection, may be responsible for: (Answer as many as apply.)
   a. acute military tuberculosis.
   b. gummatous tuberculosis.
   c. lupus vulgaris.
   d. papulo-necrotic tuberculid.
   e. tuberculous chancre.
   f. tuberculosis verrucosa cutis.

2) Exogenous inoculation, due to the direct inoculation of *Mycobacterium tuberculosis* into the skin of a person who has been previously infected but is susceptible to infection, is most likely to be responsible for: (Choose the single best response.)
   a. acute military tuberculosis.
   b. gummatous tuberculosis.
   c. lupus vulgaris.
   d. papulo-necrotic tuberculid.
   e. tuberculous chancre.
   f. tuberculosis verrucosa cutis.

3) Which of the following is widely described as the most common form of cutaneous tuberculosis? (Choose the single best response.)
   a. Acute military tuberculosis
   b. Gummatous tuberculosis
   c. Lupus vulgaris
   d. Papulo-necrotic tuberculid
   e. Tuberculous chancre
   f. Tuberculosis verrucosa cutis

4) The most accepted mode of development of tuberculosis cutis orificialis is: (Choose the single best response.)
   a. direct spread from adjacent organs.
   b. hematogenous spread.
   c. ingestion of bacilli in sputum.
   d. lymphatic spread.
   e. exogenous inoculation due to the direct inoculation of *Mycobacterium tuberculosis* into the skin/mucosa of a person who is susceptible to infection.

5) “Apple-jelly” nodules present on the head and neck of individuals in Western countries are most characteristic of: (Choose the single best response.)
   a. erythema induratum of Bazin.
   b. lichen scrofulosorum.
   c. lupus vulgaris.
   d. papulonecrotic tuberculid.
   e. tuberculosis verrucosa cutis.

ANSWERS TO SELF-TEST REVIEW QUESTIONS:
1) c, e, f; 2) f; 3) c; 4) c; 5) c

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E-mail: lamberwc@umdnj.edu

RESTLESS LEG SYNDROME

Drugs that may cause restless leg syndrome (RLS)

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<td>Dilantin</td>
<td>Neurotin</td>
<td>Seroquel</td>
<td>Zyprexa</td>
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<tr>
<td>Elavil</td>
<td>Paxil</td>
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<td></td>
</tr>
</tbody>
</table>

Adapted from Litt, JZ. *Curious, Odd, Rare, and Abnormal Reactions to Medications*. Fort Lee, NJ: Barricade Books; 2009:107.
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Repelling Insects With Safe and Effective Alternatives to DEET

Howard A. Epstein, PhD

In addition to the annoying itch that results from biting insects, insect-borne diseases, including Lyme disease, encephalitis, Rocky Mountain spotted fever, and West Nile virus, are all causes of concern for many individuals who wish to enjoy the outdoor environment during the warmer months of the year. The military of various nations experienced the same problems and have conducted much research in developing repellents to protect their soldiers. The Indian Army used oils of citronella, camphor, and paraffin as repellents. These agents were effective for limited periods and therefore the search for more effective repellents continued. In 1953, N, N-diethyl-m-toluamide (DEET) was discovered (Figure 1). As of 2007, it was estimated that 15 million people in the United Kingdom, 78 million people in the United States, and 200 million people globally use DEET each year.1 Over the years, as cases of insect-borne diseases continued to be reported in the news, so has the use of DEET. Reports of adverse reactions associated with DEET have increased with its use.

HEALTH-RELATED ISSUES AND CONSUMER CONCERNS

In 2004, the Oregon State University (OSU) Agricultural Experiment Station issued a press release entitled “OSU Scientist Gives Safety Tips for Use of DEET Against Mosquitoes & West Nile Virus.” In the release, Dr Daniel Sudakin, an assistant professor at OSU’s Department of Environmental and Molecular Toxicology and toxicologist at the Agricultural Experiment Station was quoted as expressing concern that hundreds of adverse reactions, most commonly affecting the skin, are reported each year. The majority of these adverse reactions occur when DEET is overused or misused.2 In 2009, Science Daily published a paper entitled “Popular Insect Repellent DEET Is Neurotoxic.”3 The contribution referenced a study that concluded that DEET is not simply a behavior-modifying chemical, but also inhibits the activity of a key central nervous system enzyme, acetylcholinesterase, in both insects and mammals.4

In 2004, the Agency for Toxic Substances & Disease Registry issued a report on the health effects of DEET in humans. The report mentioned 6 cases of DEET ingestion, 3 led to death after ingestion of 15 mL to 50 mL of 47.5% to 95% DEET filled in bottles. In 2 of these cases, the individuals drank an unspecified amount of alcohol. In the third case, the individual ingested an unspecified number of pills with 50 mL of DEET. In yet another case, a woman ingested 15 mL to 25 mL of 95% DEET and was admitted to a hospital with right and left atrial enlargement that returned to normal within 24 hours. This woman survived with no further cardiac abnormalities.5 From 1961 to 2002, the Agency reported 8 deaths related to DEET exposure, 3 resulting from deliberate ingestion, and 2 following dermal exposure to DEET. The remaining 3 cases were girls aged 17 months, 5 years, and 6 years. All 3 children were described as having “heavy, frequent, or nightly applications of DEET.” The 6-year-old had congenital ornithine carbamoyl transferase deficiency, which may have contributed to her death.2 Two other reported cases involved 2 men, aged 27 and 30 years, who developed severe psychological effects from exposure to DEET. In both cases, the men recovered after hospitalization.5

MILITARY AND GOVERNMENT PERSONNEL: DERMAL EFFECTS OF DEET EXPOSURE

Unique cutaneous side effects were reported in 15 soldiers who applied military-issued DEET repellents. One soldier applied a 33% DEET repellent to his skin without washing it off at bedtime. He developed a vesiculobullous eruption, which cleared after 14 days. Another soldier who went to bed without removing DEET applied to his skin woke up 8 hours later complaining of a burning sensation and skin eruptions. A 10-day treatment with corticosteroids cleared the condition. Other soldiers reported burning skin and erythema after application of 50% DEET solution applied just before bedtime. Three soldiers were referred to treatment by a dermatologist: 2 of the soldiers developed a permanent scar and 1 required corrective surgery.5
Other controlled studies in which DEET was applied to 63 volunteers with a gauze pad soaked in DEET determined that DEET should be washed from skin prior to sleeping directly related to the irritant effects of DEET. Additional studies involving 143 National Park Service employees at Everglades National Park resulted in 36 of the workers having adverse health effects to the applied DEET. The effects included skin or mucous membrane irritation, transient numb or burning lips, dizziness, disorientation, and difficulty in concentration. Headache and nausea were also reported.

MULTIPLE CASE STUDIES OF DEET EXPOSURE

An analysis of phone calls to poison control centers in the United States from 1985 to 1989 represented more than 6 million human exposures to a variety of chemicals. Of these, 9086 were related to DEET. Of the DEET-related calls, 54% of patients had no symptoms at the time of the call and 40% had symptoms thought to be related to DEET exposure. The most commonly reported exposure was inhalation of DEET or spray into the eyes. These exposures were more likely to cause adverse reactions compared with cases in which small quantities of DEET were ingested. Of the individuals with symptoms, 88% did not require medical attention, 35% had minor skin irritation, and 1% experienced disorientation or brief seizures. There was a reported death from deliberate consumption of an 8-oz bottle of DEET. Children were not more likely to develop side effects than adults.

CASE REPORTS OF CHILD EXPOSURES

During 1961 to 2002, 14 of the 17 reported cases of significant DEET toxicity were in children younger than 8 years. The most frequently reported symptoms of DEET toxicity in children were lethargy, headaches, tremors, involuntary movements, seizures, and convulsions. The common route of exposure in children is frequently dermal or accidental ingestion. Adverse effects have been reported in an 18.5-month child who was sprayed with 20% DEET daily for 3 months and a 6-year-old who was sprayed with 15% DEET on 10 occasions. Generally, children recover from exposure. In 1989, there were 4 cases of children ages 3 to 7 years and a 29-year-old man having generalized seizures associated with the dermal application of DEET, with fewer than 3 applications.

ALTERNATIVES TO DEET

Picaridin, 1-piperidine carboxylic acid-2(2-hydroxyethyl)-1-methpropylester (Figure 2) was developed by Bayer in the 1980s. It is a synthetic molecule chemically based on the active agent in pepper (Piper sp). Picaridin was first registered with the US Environmental Protection Agency (EPA) in 2001 and entered the market in 2005. Picaridin has a favorable safety profile, most likely because the compound has not been as commercially available for as long as DEET, and therefore there is far less information regarding adverse reactions.

The first report of a contact allergy during commercial use was reported in 2005, in which a 39-year-old man experienced an itchy erythematous reaction to a spray a few hours after application to the skin. Australian soldiers evaluated 19.2% Picaridin compared with 35% DEET in a gel formulation, with significantly more soldiers reporting mild discomfort and irritation with the use of the DEET gel. Published studies indicate that Picaridin may be as effective as DEET. There are variations in repellent efficacy depending on species of insect and levels of use. The literature reports that Picaridin is aesthetically more “elegant” than DEET in various formulations.

NATURAL AND EFFECTIVE ALTERNATIVES

IR3535, [3-(N-acetyl-N-butyl)aminopropionic acid ethyl ester] (Figure 3) has been marketed by Merck KGaA, Darmstadt, Germany, for the past 30 years. It was registered by the US EPA in 1999. IR3535 is unique in that it is classified as a biopesticide repellent. DEET and Picaridin are classified as conventional insect repellent pesticides. The EPA defines a biopesticide as a pesticide derived from natural materials including animal, plant, bacteria, and minerals. Canola oil and baking soda have pesticidal applications and are considered biopesticides.

Biochemical pesticides are naturally occurring substances that control pests.
by nontoxic mechanisms. The EPA has established a special committee to determine the most appropriate classification based on established criteria.7

Biopesticides are usually less toxic than conventional pesticides. They generally affect only the target pest and closely related organisms compared with broad-spectrum conventional pesticides that may affect other organisms including birds and mammals.7 IR3535 received this classification because it is functionally identical to naturally occurring β-alanine. It is a substituted B amino acid that contains 98% 3-(N-acetyl-N-butyl) aminopropionic acid, ethyl ester as an active ingredient and 2% inert ingredients. The end groups are not likely to contribute to toxicity and it acts to control the target pest via a nontoxic mode of action.7 In various studies, IR3535 has been shown to be as effective as DEET. As with Picaridin the formulation, level of repellent, and species of insect may be a factor with respect to repellent efficacy.1 IR3535 is also reported to be more cosmetically elegant than DEET when evaluated in various human studies. As of publication in 2007, the authors of Insect Repellents: Principles, Methods, and Uses claim there were no reported adverse reactions to IR3535.1 IR3535 is registered for use as an insect repellent against mosquitoes, deer ticks, body lice, and biting flies. The formulated products are applied directly to skin. The low toxicity data for IR3535 implies that there is reasonable certainty of no harm for the general population, as well as subgroups including infants and children.7

REVIEW OF TOXICITY DATA FOR DEET, PICARIDIN, AND IR3535

Tables I and II review toxicological data obtained from various sources. Regarding safety classification, the World Health Organization (WHO) classification for IR3535 is hazard class U, indicating that the compound is unlikely to present acute hazard in normal use.8 The WHO classified Picaridin as class III, indicating a slight hazard.9,10 DEET was also designated as class III by the WHO.12,13

### Table I. Comparative Toxicology Data for IR3535,7,8 Picaridin,9 and DEET10

<table>
<thead>
<tr>
<th>Test</th>
<th>IR3535</th>
<th>Picaridin</th>
<th>DEET</th>
<th>Reported Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute toxicity oral rat (lethal dose, 50%)</td>
<td>&gt;5000</td>
<td>2236</td>
<td>2170</td>
<td>mg/kg body weight</td>
</tr>
<tr>
<td>Acute dermal toxicity rabbit or rat (lethal dose, 50%)</td>
<td>&gt;3000</td>
<td>&gt;2000</td>
<td>4280</td>
<td>mg/kg body weight</td>
</tr>
<tr>
<td>Acute inhalation (lethal dose, 50%)</td>
<td>&gt;5.1</td>
<td>&gt;4.3</td>
<td>NA</td>
<td>mg/L</td>
</tr>
<tr>
<td>Eye irritation in rabbit</td>
<td>Irritating to eye</td>
<td>Moderate irritant</td>
<td>Irritating</td>
<td></td>
</tr>
<tr>
<td>Skin sensitization in guinea pig</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Dermal sensitization human (NOEL)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>mg/kg/d</td>
</tr>
<tr>
<td>Subchronic dermal rat (NOEL)</td>
<td>3000</td>
<td>200</td>
<td>300</td>
<td>mg/kg/d</td>
</tr>
<tr>
<td>Developmental rat (oral)</td>
<td>1000</td>
<td>400</td>
<td>250</td>
<td>mg/kg/d</td>
</tr>
<tr>
<td>Ames test (Salmonella typhimurium)</td>
<td>Nonmutagenic</td>
<td>Nonmutagenic</td>
<td>Nonmutagenic</td>
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<tr>
<td>Micronucleus assay</td>
<td>Nonmutagenic</td>
<td>Nonmutagenic</td>
<td>Nonmutagenic</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DEET, N, N-diethyl-m-toluamide; NA, not applicable; NOEL, no observed effect level. Higher scores indicate lower potential for toxicity.

### Table II. Information From Various EPA Fact Sheets5,7,9

<table>
<thead>
<tr>
<th>EPA FACT SHEET CLASS</th>
<th>IR3535</th>
<th>Picaridin</th>
<th>DEET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inhalation toxicity</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>Primary dermal irritation</td>
<td>IV</td>
<td>IV</td>
<td>III</td>
</tr>
<tr>
<td>Acute oral</td>
<td>IV</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Acute dermal</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Primary eye</td>
<td>II</td>
<td>III</td>
<td>III</td>
</tr>
</tbody>
</table>

Abbreviations: DEET, N, N-diethyl-m-toluamide; EPA, Environmental Protection Agency. Category I, very highly or highly toxic; category II, moderately toxic; category III, slightly toxic; category IV, practically nontoxic.
CONCLUSIONS
Insect repellents are more effective at higher concentrations. In addition to the level of actives in the formulation, the degree of efficacy may be related to the species of insect to be repelled. Another factor is proper use of the repellent. When there is concern that label directions for use may not be properly followed, the best option is to suggest the compound with the least hazard risk. The WHO notes that classification criteria are guide-points intended to supplement but never substitute for special knowledge, sound clinical judgment, or experience with a compound.13

REFERENCES
Leiomyosarcoma of the skin is a rare soft tissue neoplasm of smooth muscle origin. Treatment and prognosis of this lesion are dependent on its depth, with deep soft tissue tumors carrying a significantly worse prognosis and requiring more extensive surgery than cutaneous ones. It is essential that all physicians involved know this. It is also critical that the dermatopathologist report the depth of a leiomyosarcoma in order for the clinician to render appropriate therapy. Failure to report the location of this neoplasm and/or failure to comprehend the prognostic significance of this information, can lead to inappropriate therapy and increased morbidity in patients.

**CLASSIFICATION**

Three classifications of smooth muscle tumors of the skin have been described:

- Atypical smooth muscle tumor of the dermis (purely dermal lesion);
- Cutaneous leiomyosarcoma (dermal lesion with minimal extension into the subcutis);
- Subcutaneous leiomyosarcoma.

Microscopically, the cutaneous leiomyosarcoma lesion involves the dermis and focally, the subcutis. It is composed of blunt-ended, cigar-shaped fusiform neoplastic spindle cells with eosinophilic cytoplasm forming fascicles and bundles. This neoplasm may appear in two different architectural patterns: a fasciculated growth pattern and a pilar-type architectural pattern (Figure 1 and Figure 2). The latter generally represents a low-grade neoplasm showing histologic features suggestive of pilar leiomyoma with the addition of a variable degree of cytological atypia and mitoses.

**CLINICAL FINDINGS**

Cutaneous leiomyosarcomas typically follow an indolent clinical course. Local recurrence does occur; however, distant metastasis is uncommon and mortality related to tumor progression is unusual. In contrast to cutaneous leiomyosarcoma, subcutaneous leiomyosarcoma presents as a larger mass of a higher grade. Although still superficially located above the fascia, the local recurrence rate and metastatic rate of subcutaneous leiomyosarcoma is closer to the more ominous deep soft tissue leiomyosarcoma.

Based on the differences in their prognoses, investigators proposed the term *atypical intradermal smooth muscle neoplasm* instead of cutaneous leiomyosarcoma to highlight the benign nature of cutaneous leiomyosarcoma vs the more aggressive soft tissue leiomyosarcoma and subcutaneous leiomyosarcoma. The same group also argued that grading primary dermal atypical smooth muscle neoplasms is inappropriate given the fact that the only prognostic predictor is margin status at the time of excision and no other reliable prognostic factor has been identified. While we respect these investigators’ opinion, we believe that thus terming such lesions is a bit like a tail wagging the dog. We believe it is more sensible to name a tumor in the most logical way based on its histological features, and subsequently to note if some subset of these lesions has a different prognosis.

**TREATMENT**

Treatments for cutaneous and deep soft tissue leiomyosarcoma differ significantly. Unlike deep soft tissue leiomyosarcoma, which requires extensive surgery, the standard treatment for cutaneous leiomyosarcoma and subcutaneous leiomyosarcoma is wide local excision, with margins ranging from 2 cm to 5 cm. Mohs’ micrographic surgery (MMS) has also been used for cutaneous leiomyosarcomas. This technique can be beneficial as it provides the ability to examine all margins as the lesion is excised while sparing normal tissue. At this time, only a few small studies investigating MMS have been reported and further studies are required to investigate this technique.
OBSERVATIONS

Due to the increased risk of metastasis and the worse prognosis of subcutaneous leiomyosarcoma, an analysis of the subcutaneous tissue is crucial when the diagnosis of cutaneous leiomyosarcoma is made. Undergrading of the tumor may occur if a shave biopsy is utilized to diagnose the lesion.

In contrast to deep soft tissue leiomyosarcomas, which may require extensive surgery, overly aggressive treatment or mutilating surgeries are not warranted in cutaneous leiomyosarcoma. The standard of care for cutaneous leiomyosarcoma remains wide excisional biopsy; however, recent studies have shown benefits to using MMS.

The dermatopathologist must report the depth of the tumor and the closest distance from the margin in order to provide the best therapeutic approach. The clinician must then understand the significance of this interpretation. Failure to distinguish and report the exact depth of this neoplasm or a failure of the clinician to understand the significance of this information may lead to inappropriate and aggressive treatment with excess morbidity.

REFERENCES

It May Be Vulgar, but It Isn't a Bad Word

David Saunders, MD;1,2 Thomas Herchline, MD;2 Jack M. Bernstein, MD1,2

A 38-year-old immigrant from Costa Rica presented with a 3-year history of right ear ulcerations with associated intermittent scant, bloody pururulent drainage. There was no antecedent trauma and no fevers, chills, night sweats, or weight loss. Six months previously, QuantiFERON-TB Gold testing (Cellestis Limited, Chadstone, Melbourne, Victoria, Australia) was positive and the chest x-ray was negative. He was not treated for latent tuberculosis (TB). On physical examination, the patient was afebrile and his vital signs were stable. A firm, shallow, and crusted right helix and lobule ulcerations were present (Figure 1). Abdominal examination revealed left upper quadrant tenderness and splenomegaly. Skin biopsy results of the right lobule showed mixed inflammatory infiltration with lymphocytes, plasma cells, and epitheloid cell histiocytic noncaseating granulomas (Figure 2). Results from acid-fast bacilli (AFB) and fungal stains were negative. Polymerase chain reaction for TB was negative. The presumptive diagnosis of lupus vulgaris was made, and isoniazid, rifampin, ethambutol, and pyrazinamide were started. A month and a half after starting treatment, the lesions regressed and drainage ceased (Figure 3). The patient continued 4-drug treatment for 2 months followed by 4 months of isoniazid and rifampin.

Cutaneous TB is rarely diagnosed, even in countries in which a high prevalence of TB is present. In a Spanish dermatology center, the incidence of cutaneous TB during 13 years was 0.14%.1 Variants of cutaneous TB include primary-inoculation TB, TB verrucosa cutis, lupus vulgaris, scrofuloderma, miliary TB of the skin, orificial TB, and tuberculids.2 Lupus vulgaris is the most common type of cutaneous TB, representing 55% of cutaneous TB cases during 20 years in India.3 Lupus vulgaris usually occurs as a result of hematogenous, lymphatic, or direct spread from visceral TB. Inoculation after trauma occurs less commonly.3

CLINICAL MANIFESTATIONS

The clinical presentation of lupus vulgaris is often nonspecific. Patients most commonly present with chronic ulcerating and scarring lesions that persist for 2 to 3 decades before diagnosis.4 In an Indian study, nearly one third of patients with lupus vulgaris presented 5 years after disease onset.5 Lesions typically began as flat and red-brown papules that enlarged to form erythematous and violaceous plaques with atrophic centers and firm raised edges. Diazacyclophosphamide reveals a characteristic “apple-jelly” color.6 Lesions most commonly involve the head and neck,7 particularly the nose and ears.1

DIAGNOSIS

Hematoxylin and eosin staining of skin biopsy tissue shows epidermal hyperplasia and hypertrophic changes involving the upper and mid dermis. Epitheloid cell granulomas and lymphocytes predominate. Caseation necrosis is rarely present. Results from Lovenstein-Jensen culture and Ziehl-Neelsen staining of specimens are often negative.3,4 Only 3 of 44 patients with lupus vulgaris had AFB–positive skin biopsy specimens in two combined Indian studies.3,4 Tuberculin skin testing and interferon gamma release assays may be helpful but are not diagnostic. If cutaneous TB is suspected but not confirmed, clinical improvement with empiric antituberculous therapy confirms the diagnosis.

TREATMENT

As the number of bacilli in cutaneous TB is small, 6 months of treatment for cutaneous TB is likely adequate. Standard therapy would include isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months followed by isoniazid and rifampin for 4 months.6,7 Evidence of TB at other sites should be excluded before starting antituberculous medications. If Mycobacterium tuberculosis is isolated from another site, it should be tested for resistance.3

CONCLUSIONS

Cutaneous TB is a challenging diagnosis that is uncommon even in high-prevalence regions for TB. Lupus vulgaris is a variant of cutaneous TB that is particularly difficult to diagnose given its nonspecific clinical presentation and the relative
difficulty in isolating AFB from skin biopsy specimens. In this report, historical clues to the diagnosis of cutaneous TB included immigration from an endemic region for TB and positive QuantiFERON-TB Gold testing (Cellestis Limited, Chadstone, Melbourne, Victoria, Australia). Rapid clinical improvement with empiric antituberculous therapy confirmed the diagnosis of lupus vulgaris when physical examination findings and histopathology were nonspecific. In an era in which TB infects much of the world’s population, clinicians should have a high clinic suspicion for cutaneous TB in patients with characteristic skin lesions and risk factors for TB exposure.

REFERENCES

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The term dermatosis neglecta was originally coined in 1995 when three cases of an “unwashed dermatosis” were presented by L. Poskitt and colleagues. In all cases, the patients committed what Poskitt described as “acts of omission” by failing to wash their skin in the affected areas. The resulting hyperpigmented, hyperkeratotic dermatosis resolved by vigorously washing with soap and water or, in severe areas, by applying 5% salicylic acid in aqueous cream twice daily. Our patient had a severe case that responded well to salicylic acid followed by routine washing. Because the patient was subsequently lost to follow-up, we were unable to evaluate hair regrowth.

Periodic shedding of the outermost cellular layers is an essential component of normal keratinocyte development. In the stratum corneum, protein-rich, lipid-depleted keratinocytes are the “bricks” that are held together by hydrophobic intercellular membranes and desmosomes, making up the “mortar.” Genetic defects in this system—either in the keratinocytes themselves or their intercellular molding—can lead to abnormal retention of stratum corneum, causing disorders such as ichthyosis vulgaris and recessive X-linked ichthyosis. Ichthyosis vulgaris is caused by defective profilaggrin, a keratinocyte protein, and recessive X-linked ichthyosis is caused by a deficiency in steroid sulfatase, an enzyme in the intercellular domain. These genetic abnormalities of adherent stratum corneum illustrate the importance of regular shedding of superficial keratinocyte layers.

Dermatosis neglecta represents a failure to cleanse adequately a particular area of skin, leading to the buildup of adherent hyperpigmented scales. Thus, dermatosis neglecta can be understood as a self-induced “defect” in normal keratinocyte shedding that causes abnormal accumulation of cellular layers and debris. Dermatosis neglecta typically occurs in an area of hyperesthesia or prior trauma where the patient refuses to scrub the skin. Also, as in our patient, dermatosis neglecta can develop in situations where a patient is unable to properly care for an area of skin because of physical or mental disability.

A similar condition described in the literature is terra firma forme dermatosis (TFFD), which is a disorder of unknown etiology characterized primarily by disordered keratinization. In TFFD, the classic clinical finding is a dark, dirty-looking, slightly raised hyperkeratotic skin lesion that is completely asymptomatic. Cases of TFFD respond to 70% isopropyl alcohol rubs but not to cleansing with normal soap and water; therefore, TFFD can be distinguished from dermatosis neglecta.

CASE STUDY
Vesna Petronic-Rosic, MD, MSc, Section Editor

Unusually Severe Case of Dermatosis Neglecta
Jake E. Turrentine, BS; Travis W. Blalock, MD; Loretta S. Davis, MD

An 18-year-old black woman with cerebral palsy was admitted for evaluation of an intrathecal baclofen pump site infection. The dermatology service was consulted for treatment suggestions of a presumed diagnosis of chronic tinea capitis. Three courses of oral griseofulvin during the past 2 years failed to resolve the patient’s chronic scalp dermatosis. Scalp lesions first began about 2 years earlier after hospitalization for placement of an intrathecal baclofen pump. The patient was unable to care for her scalp due to her cerebral palsy, and her mother interpreted the scalp condition as infectious. No routine shampoo care, scalp care, or topical treatment was performed for more than 1½ years. The mother felt that touching the patient’s scalp might cause pain and noted that the majority of her time was spent concentrating on more critical medical issues. Physical examination revealed coalescing hyperkeratotic plaques extending dorsally from the anterior hairline to the occipital scalp with small flecks of keratinous debris throughout the remaining hair (Figure 1). The plate-like plaques were devoid of hair, except at a few fissures where a few tufts of hair emerged. No cervical lymph nodes were appreciated on palpation. Treatment was initiated with compresses consisting of large warm water–soaked towels 4 times daily. Three times a day, a nursing staff applied 5% salicylic acid in olive oil to the scalp under a shower cap for approximately 1 hour. Over the following 2 days, a significant reduction in keratinous debris was appreciated. Within 2 weeks, the bulk of the plaques had been removed (Figure 2). At 6-week follow-up, the underlying scalp showed areas of fibrosis and possible scarring with a few emerging tufts of hair. On the basis of history and response to treatment with salicylic acid and routine scalp care, the patient was diagnosed with an unusually severe case of dermatosis neglecta.
clinically from dermatosis neglecta by the lack of response to normal washing and, of course, the absence of historical clues of neglect.

Given its rapid response to inexpensive and simple treatment, dermatosis neglecta should be considered in the evaluation of a pigmented, hyperkeratotic skin lesion. If identified, a skin biopsy can often be avoided. Physicians should always inquire about skin care habits when gathering history about an unexplained skin lesion and should review and recommend normal skin hygiene, when a patient fails to respond to a full course of standard therapy for an alternate diagnosis.

REFERENCES

CASE STUDY

Fixed-Drug Eruption Caused by Ashwagandha (Withania somnifera): A Widely Used Ayurvedic Drug

Virendra N. Sehgal, MD; Prashant Verma, MD; Sambit N. Bhattacharya, MD

A 28-year-old man with decreased libido received ashwagandha in the usual daily dosage of 5 g for 10 days. During this period, he experienced a burning and/or itching sensation as well as discoloration of the skin/mucous membrane confined to the penis. He had a similar type of eruption at the same site 6 months prior while taking ashwagandha. Examination of the skin surface was conspicuous and marked by the presence of a dusky, erythematous, oval, eroded plaque of 3 cm, affecting the glans penis and prepuce (Figure). The drug was withdrawn and topical 0.05% clobetasol propionate cream was administered along with cetirizine dihydrochloride, an H1-receptor blocker, 10 mg daily for 1 month. There was a perceptible amelioration of the lesion, resulting in residual greyish white pigmentation. He was prescribed oral drug provocation with 1 g of ashwagandha powder. Within 12 hours, a flare-up developed at the earlier site, confirming the causality.

Fixed-drug eruption, one of the most well-recognized adverse drug reactions, is characterized by a peculiar, sudden onset of round and/or oval, edematous, dusky red macules/plaques on the skin and/or mucous membranes accompanied by burning and/or itching.1 Several drugs have been incriminated in its causation, the details of which have been specifically recounted in a recent comprehensive review.2 Ashwagandha belongs to an alternative system of medicine and has a long medicinal history. It is an innocuous agent that has not been associated with any cutaneous drug reactions to date. Fixed-drug eruption following the use of ashwagandha is an uncommon occurrence; hence, the current report.

Ashwagandha literally means “horse smell” (ashwa = horse, gandha = smell), for its wet roots smell similar to horse’s urine. Withania somnifera, also known as ashwanganga, Indian ginseng, winter cherry, ajagandha, kanaje hindi, and samml ferakh, the offending indigenous drug, is derived from a plant in the Solanaceae or nightshade family.3 It is a beautiful, delicate plant native to India, Pakistan, and Sri Lanka. It is considered the king of herbs among ayurvedic medicines. It has a medicinal history of 4000 years and is well-accepted, vital drug in Ayurveda and Indian traditional medicine.4 It has been conventionally used for calming the mind and relieving weakness, nervous exhaustion, and arthritis. In addition, it is used for building sexual energy. Ashwagandha root is said to be beneficial in people who do physical labor or exercise a lot, helping the body adapt to physical stress. In addition, its paste is recommended for external use in the treatment of carbuncles, ulcers, and nondescript swellings. Bedsores and wounds are also amenable to topical application of ashwagandha leaves.

CONCLUSIONS

Ashwagandha is said to possess anti-inflammatory, anti-tumor, antistress, antioxidant, immunomodulatory, hemopoeitic, and rejuvenating effects.5 In addition, it is thought to exert a positive influence on the endocrine, cardiopulmonary, and central nervous systems.6 Ashwagandha’s mechanism of action is still speculative, and toxicity studies have revealed it to be a safe compound.7-9

REFERENCES

CASE STUDY

Fixed-Drug Eruption Caused by Ashwagandha


Figure. Fixed-drug eruption affecting the glans and prepuce of the penis.
Various cutaneous lesions may appear at sites of prior herpes zoster infection, such as annular granuloma, sarcoidal granuloma, granulomatous vasculitis, Kaposi’s sarcoma, and pseudolymphoma. These cutaneous lesions may appear immediately after resolving vesicular lesions or at varying times after the acute eruption. We describe in this report an unusual case of a granulomatous zosteriform eruption revealing B-cell chronic lymphocytic lymphoma.

Our patient is of special interest because she presented with a granulomatous eruption arising after a probable latent zoster revealing B-CLL. Unfortunately, varicella-zoster virus DNA detection was not performed in our case.

Granulomatous reactions and specific infiltrations at sites of resolved cutaneous herpes zoster lesions in patients with B-CLL have been described as a rare clinical event. The cause of granulomatous reactions caused by varicella-zoster virus remains to be elucidated. Type III and type IV hypersensitivity reaction, isotopic response, and viral etiologies are thought to be possible provoking factors. A study of granulomatous reactions associated with herpes zoster lesions for the presence of varicella-zoster virus genome using the polymerase chain reaction suggested that varicella-zoster virus DNA is detected in cases where eruption occurred immediately in the wake of resolving vesicular herpes zoster lesions. In this case, differential diagnosis includes specific cutaneous infiltrates with neoplastic B cells. The clinical resolution of the lesions after treatment with acyclovir and topical steroids confirms the benign nature of the granulomatous infiltration.
CONCLUSIONS

An atypical zosteriform eruption should alert dermatopathologists to the possibility of an associated hematological dyscrasia, mainly B-CLL.

REFERENCES

Figure 2C. The majority of infiltrating cells staining positively with the pan–T-cell marker CD3 (CD 3 staining [Novocastra, Newcastle upon Tyne, UK], original magnification ×40).

Figure 2D. The infiltrating cells staining positively with the pan–B-cell marker CD20 (CD 20 staining [DakoCytomation, Glostrup, Denmark], original magnification ×40).


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To the Editor:

*Mycobacterium marinum* is an aerobic, waterborne mycobacte-
rium commonly found in nonchlorinated water in a worldwide
distribution. It is also the most common atypical Mycobacte-
rium to cause infection in humans. Infection is not transmittable
from person to person, and skin infections due to *M marinum*
are rare.1

There is no established treatment of choice for *M marinum*
infection, probably because it is a multidrug-resistant species.
Its treatment has been based primarily on personal experience
without the benefit of large studies.2 To our knowledge, this is
the first case of cutaneous *M marinum* infection treated with
azithromycin monotherapy.

A 52-year-old-woman, a cleaning worker in our hospital, was
referred to our department because of the appearance of red
nodules on the left palm and left forearm in a sporotrichoid
distribution (Figure 1). She mentioned that the first lesion
appeared on her hand 6 months previously and new lesions
gradually appeared and increased in number and size during this
period. She also reported a private fish aquarium usually cleaned
by her without using hand protection. The remainder of her
medical history was unremarkable.

Routine laboratory tests including human immunodeficiency
virus test were within normal limits. The patient underwent
surgical skin biopsy of the nodule of the forearm, and histologic
examination revealed the presence of tuberculoid structures with
neutrophils and macrophages (Figure 2). Results from periodic
acid-Schiff and Ziehl-Neelsen stains were negative. Cultures taken
from the lesions were negative for bacilli or atypical mycobacteria.

Chest and right hand radiological evaluations were normal. The
patient reported an episode of headache after doxycycline intake,
a ciprofloxacin-associated morbilliform eruption, and frequent
gastrointestinal symptoms after drug administration. She told
us she could receive azithromycin without a problem; there-
fore, we decided to try azithromycin 500 mg (tabs Zinfect
500 mg, Verisfield, Athens, Greece) 3 times a week for 2 months
and re-evaluation. To our surprise, complete clinical cure was
obtained after 8 weeks of treatment (Figure 3). No relapse has been
observed after 10 months of follow-up.

*M marinum* infection, also called “fish tank granuloma,”
“aquarium granuloma,” or “swimming pool granuloma” seems to
represent an opportunistic disease and occurs after approximately
2 weeks of direct (traumatic) inoculation of the organism either
from fish fins and bites or from the handling of aquariums.3

Solitary red-to-violaceous plaques or nodules with an overlying
crust or verrucous and/or ulcerate surface is a common clinical
presentation in immunocompetent patients. Inflammatory

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![Figure 1](image1.png)

*Figure 1.* *Mycobacterium marinum* skin infection of the left palm with sporotrichoid distribution on the left forearm.

![Figure 2](image2.png)

*Figure 2.* Histologic examination revealed the presence of tuberculoid structures (hematoxylin and eosin stain, original magnification ×100).
nODULES, abscesses with a sporotrichotic type of distribution, followed by nodular lymphangitis can develop in severely immunosuppressed patients. Over a period of months, involvement of deeper soft tissues (tenosynovitis, arthritis, bursitis, and/or osteomyelitis of the underlying bone) may be life-threatening. Lesions may be either painful or painless. Lung involvement, disseminated infection, and bacteremia have been rarely reported.

The organism can be isolated from the lesion as well as from infected fish or aquariums; however, in clinical practice, diagnosis remains largely presumptive based on clinical-histologic features. Histopathologic examination usually reveals a nonspecific inflammatory infiltrate.

Treatment of *M. marinum* infections is challenging. In superficial cutaneous infections, minocycline, clarithromycin, doxycycline, trimethoprim sulfamethoxazole, and ciprofloxacin as monotherapy are usually effective treatment options. In severe infections, a combination of rifampicin and ethambutol seems to be the recommended regimen. Surgical treatment is usually unnecessary, and where it should be performed must be cautiously determined.

Azithromycin shows good response in vitro against other than *Mycobacterium tuberculosis* mycobacteria. There is only one case of *M. marinum* infection in a patient who underwent lung transplantation successfully treated with surgical removal of the lesions and a 12-month administration of a combination of azithromycin and ethambutol.

Azithromycin seems to be a promising option to treat *M. marinum* skin infections, although, further studies—or at least cases—are needed to establish the effectiveness of the drug.

**REFERENCES**


—Efstathios Rallis, MD, PhD, Department of Dermatology, Veterans Administration Hospital (NIMTS), Athens; Evangelos Falidas, MD, 1st Department of General Surgery, Veterans Administration Hospital (NIMTS), Athens; Panagiotis Stavropoulos, MD, PhD, Department of Dermatology, University of Athens, “A.Syggros” Hospital, Athens, Greece

**Figure 3.** Complete clearance of the lesions was achieved after 8 weeks of azithromycin treatment.

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BRIEF SUMMARY

INDICATIONS AND USAGE
Locoid Lipocream is a topical corticosteroid indicated for: relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults and the treatment of mild to moderate atopic dermatitis in patients 3 months to 18 years of age.

WARNINGS AND PRECAUTIONS
Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticoid insufficiency. Consider periodic evaluations for HPA axis suppression if Locoid Lipocream is applied to large surface areas or used under occlusion. If HPA axis suppression is noted, reduce the application frequency, discontinue use, or switch to a lower potency corticosteroid. Systemic effects of topical corticosteroids may also include manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infections develop. Discontinue use if irritation develops.

ADVERSE REACTIONS
The most common adverse reactions (>1%) are HPA axis suppression and application site reactions.
The following additional local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions included: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, miliaria and telangiectasia.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women. Therefore, Locoid Lipocream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Please refer to full prescribing information for detailed information regarding systemic embryofetal development studies.

Nursing Mothers
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Locoid Lipocream is administered to a nursing woman.

Pediatric Use
Safety and efficacy in pediatric patients below 3 months of age have not been established.

Because of higher skin surface-to-body-mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at a greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing’s syndrome while on treatment.

Eighty-six (86) pediatric subjects (5 months to less than 18 years of age) with moderate to severe atopic dermatitis affecting at least 25% of body surface area (BSA) treated with Locoid Lipocream three times daily for up to 4 weeks were assessed for HPA axis suppression. The disease severity (moderate to severe atopic dermatitis) and the dosing regimen (three times daily) for which Locoid Lipocream is indicated. Five of the 82 evaluable subjects (6.1%) demonstrated laboratory evidence of suppression, where the sole criterion for defining HPA axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter after suppression, where the sole criterion for defining HPA axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter after glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing’s syndrome while on treatment.

Cushing’s syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have also been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels to an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use
Clinical studies of Locoid Lipocream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies were conducted to determine the photocarcinogenic or dermal carcinogenic potential of Locoid Lipocream. Hydrocortisone butyrate revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames test and L5178Y/TK–mouse lymphoma assay) and one in vivo genotoxicity test (mouse micronucleus assay).

No evidence of impairment of fertility or effect on mating performance was observed in a fertility and general reproductive performance study conducted in male and female rats at subcutaneous doses up to and including 1.8 mg/kg/day (0.7X maximum topical human dose [MTHD]). Mild effects on maternal animals, such as reduced food consumption and a subsequent reduction in body weight gain, were seen at doses ≥0.6 mg/kg/day (0.2X MTHD).

PATIENT COUNSELING INFORMATION
Patients using Locoid Lipocream should receive the following information and instructions:
Apply a thin layer to the affected skin two or three times daily for corticosteroid-responsive dermatoses in adults. Consult with your physician to determine if treatment is needed beyond 2 weeks. Apply a thin film to the affected skin areas two times daily for atopic dermatitis in patients 3 months of age and older.
Safety of Locoid Lipocream in pediatric patients has not been established beyond 4 weeks of use.
Rub in gently.
Avoid contact with the eyes.
Do not bandage, otherwise cover, or wrap the affected skin area so as to be occlusive unless directed by your physician.
Do not use Locoid Lipocream in the diaper area, as diapers or plastic pants may occlude the affected area.
Do not use Locoid Lipocream on the face, underarms, or groin areas unless directed by your physician.
If no improvement is seen within 2 weeks, contact your physician.
Do not use other corticosteroid-containing products while using Locoid Lipocream without first consulting your physician.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from freezing. Keep out of the reach of children.

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Reversible HPA axis suppression may occur, with the potential for corticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if applied to large surface areas or used under occlusion. Systemic effects of topical corticosteroids may also include manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their large skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infection develops. Discontinue use if irritation develops. Please see full Prescribing Information on adjacent page.

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