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RESULTS PATIENTS WANT IN A FORMULATION THAT DOES THE WORK—PRESCRIBE DIFFERIN® LOTION, 0.1% TODAY!

DIFFERIN® (adapalene) LOTION, 0.1%—THE ONLY RETINOID IN A LOTION FORMULATION

ON THE JOB WITH GENTLE EFFICACY

58.2% MEDIAN TOTAL LESION COUNT REDUCTION BY WEEK 12

TOLERABILITY PROFILE SIMILAR TO DIFFERIN® (adapalene) CREAM, 0.1%

AVAILABLE IN AN EASY-TO-USE PUMP DISPENSER

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RESULTS PATIENTS WANT IN A FORMULATION THAT DOES THE WORK—PRESCRIBE DIFFERIN® LOTION, 0.1% TODAY!

A 12-week, multicenter, randomized, double-blind, parallel-group study of patients 12 to 18 years of age with acne vulgaris (N=1075).

The most frequent adverse event reported was dryness. Erythema, stinging/burning, and scaling may also occur.†

Important Safety Information

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.

www.differin.com/HCP

Please see Brief Summary of Prescribing Information on adjacent page.
DIFFERIN® Rx only
(adapalene) Lotion 0.1%
For Topical Use Only
Not For Oral, Ophthalmic, or Intravaginal Use.

BRIEF SUMMARY

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

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

Animal reproduction studies have not been conducted with DIFFERIN Lotion. Furthermore, such studies are not always predictive of topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 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, 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 acne 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. Recommend the use of sunscreen products and protective apparel (e.g., hat) when exposure cannot be avoided.
• Moisturizers may be used if necessary; however, products containing alpha hydroxy or glycolic acids should be avoided.
• This medication should not be applied to cuts, abrasions, eczematous, or sunburned skin.
• Wax depletion should not be performed on treated skin.

CONCERNED USES

No carcinogenic 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 0-24 h) 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).

Pediatric Use

In clinical trials involving DIFFERIN Lotion, 0.1% in the treatment of acne vulgaris in patients 12 years and older. Animal reproduction studies have not been conducted with DIFFERIN Lotion. Furthermore, such studies are not always predictive of 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).

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Nursing Mothers

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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 (12, 3.9, and 12 mg/m²/day),
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VELTIN Gel—A Topical Treatment for Patients 12 Years or Older With Acne Vulgaris

Once-daily application in the evening

VELTIN Gel

- Combines the acne-fighting properties of tretinoin and clindamycin
- Contains tretinoin, solubilized in an aqueous-based gel
- Combats inflammatory and noninflammatory acne

Important Safety Information for VELTIN Gel

- VELTIN Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis
- Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. VELTIN Gel should be discontinued if significant diarrhea occurs. Severe colitis has occurred following oral or parenteral clindamycin administration. Severe colitis may result in death
- Avoid exposure to sunlight and sunlamps when using VELTIN Gel. Patients with sunburn should be advised not to use VELTIN Gel until fully recovered. Daily use of sunscreen products and protective apparel are recommended. Weather extremes (eg, wind and cold) also may be irritating to patients using VELTIN Gel
- Observed local treatment-related adverse reactions (≥1%) in clinical studies with VELTIN Gel were application site reactions, including dryness, irritation, exfoliation, erythema, pruritus, and dermatitis. Sunburn was also reported. Incidence of actively assessed local skin reactions peaked at week 2 and then gradually decreased
- VELTIN Gel should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component

Please see brief summary of Prescribing Information on the next page.
INDICATIONS AND USAGE

VELTIN Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

CONTRAINDICATIONS

VELTIN Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS

COLITIS

Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. If significant diarrhea occurs, VELTIN Gel should be discontinued.

Severe colitis has occurred following oral or parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as spasmodyl and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis.

ULTRAVIOLET LIGHT AND ENVIRONMENTAL EXPOSURE

Exposure to sunlight, including sunlamp, should be avoided during the use of VELTIN Gel, and patients with sunburn should be advised not to use the product until sunburn is fully resolved because of heightened sun sensitivity as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise caution with sun exposure. Daily use of sunscreen products and protective apparel (e.g., a hat) are recommended. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with VELTIN Gel.

ADVERSE REACTIONS

Adverse Reactions in Clinical Studies

The safety data reflect exposure to VELTIN Gel in 1,104 patients with acne vulgaris. Patients were 12 years or older and were treated once daily in the evening for 12 weeks. Observed local treatment-related adverse reactions (≥1%) in clinical studies with VELTIN Gel were application site reactions, including dryness (6%), irritation (5%), exfoliation (5%), erythema (4%), pruritus (2%), and dermatitis (1%). Sunburn (1%) was also reported. Incidence of skin reactions peaked at week 2 and then gradually decreased.

Local skin reactions were actively assessed at baseline and at the end of 12 weeks. Observed local treatment-related adverse reactions (≥1%) in clinical trials of VELTIN Gel included 2,086 patients 12-17 years of age with acne vulgaris. (See Clinical Studies (14) of full prescribing information.)

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of VELTIN Gel or the effect of VELTIN Gel on fertility. VELTIN Gel was negative for mutagenic potential when evaluated in an in vitro Ames Salmonella/Escherichia coli reverse gene mutation assay. VELTIN Gel was equivocal for clastogenic potential in the presence of an in vitro chromosomal aberration assay (e.g., HeLa). VELTIN Gel was negative for mutagenic potential when evaluated in an in vitro bone marrow mammalian chromosome (CHO) assay. However, in a dermal carcinogenicity study in mice, tretinoin applied at a dose of 5.1 μg (1.4 times the recommended clinical dose based on body surface area comparison) to mice for up to 2 years did not produce evidence of tumorigenicity.

Tretinoin: In two independent mouse studies where tretinoin was administered topically (0.025% or 0.1%) three times per week for up to two years no carcinogenicity was observed, with maximum effects of dermal amyloidosis. However, in a dermal carcinogenicity study in mice, tretinoin applied at a dose of 5.1 μg (1.4 times the recommended clinical dose based on body surface area comparison) three times per week for 20 weeks acted as a weak promoter of skin tumor formation following a single application of dimethylbenz[a]anthracene (DMBA). In a study in female SENCAR mice, papillomas were induced by topical exposure to DMBA followed by promotion with 12-O-tetradecanoyl-phorbol 13-acetate or mezerein for up to 20 weeks. topical application of tretinoin prior to each application of promoting agent resulted in a reduction in the number of papillomas per mouse. However, papillomas resistant to topical tretinoin suppression were at higher risk for pre-malignant progression.

Tretinoin has been shown to enhance photocarcinogenicity in properly performed specific studies, employing concurrent or intercurrent exposure to tretinoin and UV radiation. The photocarcinogenic potential of the clindamycin tretinoin combination is unknown. Although the significance of these studies to humans is not clear, patients should avoid exposure to sun.

PATIENT COUNSELING INFORMATION

[See FDA-approved Patient Labeling in full prescribing information.]

Instructions for Use

- At bedtime, the face should be gently washed with a mild soap and water. After patting the skin dry, apply VELTIN Gel as a thin layer over the entire affected area (excluding the eyes and lips).
- Patients should be advised not to use more than a pea sized amount to cover the face and not to apply more often than once daily (at bedtime) as this will not make for faster results and may increase irritation.
- A sunscreen should be applied every morning and reapplied over the course of the day as needed. Patients should be advised to avoid exposure to sunlight, sunlamp, ultraviolet light, and other medicines that may increase sensitivity to sunlight.
- Other topical products with a strong drying effect, such as abrasive soaps or cleansers, may cause an increase in skin irritation with VELTIN Gel.

Skin Irritation

VELTIN Gel may cause irritation such as erythema, scaling, itching, burning, or stinging.

COLITIS

In the event a patient treated with VELTIN Gel experiences severe diarrhea or gastrointestinal discomfort, VELTIN Gel should be discontinued and a physician should be contacted.

VELTIN is a trademark of Astellas Pharma Europe B.V.
A 2010 publication called “International Review. Pressure Ulcer Prevention: Pressure, Shear, and Microclimate in Context,”1 attempts to provide a global consensus about the extrinsic causes and prevention of decubitus ulcers (DUs). This is a laudable aim, because these lesions remain a major health care problem. Witness the penalties inflicted when a hospital patient develops even a lone DU.

The document in question is a useful distillation of many recent contributions that discuss the causes and prevention of the DU. Even so, parts of the new document are questionable, and this particularly applies to some comments on the pressure-time curve devised by Reswick and Rogers (R&R curve).2 Pressure in this context means “uniaxial” pressure (pressure in one direction).

Arguably, prolonged tissue distortion by pressure (or related forces) is the chief extrinsic factor in the etiology of the DU. It is important to know in healthy persons just what levels of pressure and their duration are critical. The R&R curve attempted to do this, and it appeared to be showing an inverse relationship between pressure and time. The R&R curve was neither complete nor absolute,2 with their published figure (Figure 1) indicating their degree of uncertainty about a definitive curve; however, the new idea about a sigmoid function curve1,4,5 merits our consideration.

**PROBLEMS WITH CURVES**

Developing a practical pressure-time curve is problematic. For instance, in 1995 one of us (PTL) showed how the experimental pressure work of Lindan on rabbit ears6 could be reconciled with the similar work by Kosiak7,8 (Lindan and Kosiak were mid-20th century pioneers in the field). Briefly, Lindan's pressure indenters, which were rigid but smooth pads, were placed a short distance above the rabbits' hearts, thereby, acting on a reduced blood pressure, when compared with the recumbent dogs used by Kosiak, who had applied pressure to the dogs' femoral trochanters.

With this insight, a new curve was drawn (Figure 2).9 It resembled the R&R curve but was largely based on Kosiak's own pressure-time curve.8 This has been considered relevant to humans, even though dogs were used.

As with the R&R curve, the 1995 curve was not absolute; yet, it was criticized (anonymously), because it was not a true geometric (hyperbolic) curve. This, however, was not a claim made for it. Similarly, no such claim appears to have been made for the R&R curve.2 Despite this, Gefen has shown a curve that purports to be similar to the R&R curve but is more precise.4 More bizarre is the fact that this new hyperbolic curve is then criticized for predicting DUs at 25 mm Hg, which is, of course, unlikely (see below)!9

We assume that Gefen is attempting to make a case for a pressure-time curve shaped like a reversed “S,” this contention being based on skeletal muscle experiments. In short, at very high pressures, the upper part of the R&R curve ought to change direction, so that it curves toward zero on the time scale. While we agree with this, it does not affect the usefulness of either the R&R curve or the 1995 curve. In addition, the reversed S curve supports our contention that many DUs are caused by overstretching of the microcirculation.10

In explaining this, we should consider that, in Gefen’s work, as well as in similar publications,1 there appears to be no clear conviction as to why prolonged uniaxial pressure (exacerbated, or not, by related forces, such as tissue shear and tension) produces pressure necrosis. Possibly, these investigators have not fully appreciated what pressure can do to the microcirculation.
As described in previous papers,10–12 we maintain that many DUs, especially deep ones, are caused when the pressure under a bony prominence is both high enough and sufficiently prolonged to produce distortion and lateral distraction of the soft tissues. This takes time, partly because tissue fluids and gels have to migrate through tight tissue interstices.12 These distorted tissues contain the microcirculation. In consequence, this is also distracted, until it is overstretched. Then, to seal these leaking vessels, platelets are activated and so produce multiple microthrombi, surrounding the region of maximum pressure. Acidosis, followed by tissue death, then occurs in the plaque of compressed tissue, which is now almost completely devoid of circulation.

Of course, if the pressure is high enough, capillaries and other small blood vessels will be ripped by the distraction effect so that a contusion results. At even higher pressures, the skin and subcutaneous tissue are torn apart, producing a laceration. In summation, DUs, contusions, and lacerations are all related. As these very high pressures are applied to soft tissues, pressure-time curves will change direction: toward zero on the time scale. This change will occur at pressures higher than the 650 mm Hg shown on the 1995 curve (Figure 2). Such pressures are not generally encountered in normal clinical situations. Additionally, various tissues (eg, flaccid muscle and skin) will be disrupted at different levels of pressure. Unfortunately, the data for plotting such extended pressure-time curves are currently lacking.

When it comes to determining the pressure to which a patient is being subjected, both the R& R curve and the 1995 curve assume that measurements will be taken at the patient/support interface, using a small pressure sensor.13,14 If the patient’s bony prominence is close to the skin surface, such readings should be reliable; however, on some subjects, measurements over deep-seated prominences will register a pressure lower, at the interface, than will occur near the prominence. Groth demonstrated this principle in 1942.15 It follows that these deep pressures will need estimating.3

Groth also demonstrated that a rigid pressure indenter the same size and shape as a bony prominence will produce the same soft tissue pressures throughout the depth of tissue separating the prominence and the indenter.15 This points out that Kosiak’s experimental results, using pressure indenters similar in size and shape to the dogs’ femoral trochanters, must be very close to the actual tissue pressures the dogs experienced. It follows that the 1995 curve, being largely based on Kosiak’s curve, should indicate the maximum pressure levels and times under such pressures that can be allowed (in humans) to avoid pressure necrosis; this being for normotensive patients, at heart level.

We still await pressure-time curves for tissues situated some distance below the heart; likewise, we have no pressure-time curves for either hypotensive or hypertensive patients. Estimates are possible using data from a suitable textbook.16 Interestingly, Reswick and Rogers, along with some other researchers, probably did not appreciate that normal tissue pressures at some distance below the heart register higher than those at heart level.16,17 This may account for some of the uncertainty in their results.3

At the lower end of the 1995 pressure-time curve, there comes a point where long-continued pressures (below 50 mm Hg but...
above 32 mm Hg) should result in tissue atrophy, rather than in pressure necrosis; hence the reference to atrophy in Figure 2.

As a result, we maintain that the R&R curve, and particularly the 1995 curve, gives useful indications of the pressures and times needed to cause pressure necrosis, or tissue atrophy, in humans.

PRESSURE ON MUSCLES

In the 2010 document, and in other papers by Gefen, some emphasis is placed on the trauma to muscle cells caused by pressure. We agree that damaged muscle cells can result from prolonged pressure. Even so, the microanatomy of skeletal muscle illustrates that muscle capillaries mostly run between the fibrils. With the muscle relaxed (or flaccid) they are straight rather than convoluted. As a result, they can be easily overstretched when pressure is applied, which is an important consideration.

In practice, however, many DUs (eg, on the heels and the femoral trochanters) do not involve skeletal muscle. Similarly, this applies to the ischia because, when seated, the gluteal muscles normally slip sideways so that the specialized panniculus adiposus of the buttocks is positioned under the ischia. Even so, if an indenter presses against muscle tissue, we should expect to get trauma to the ischia because, when seated, the gluteal muscles normally slip sideways so that the specialized panniculus adiposus of the buttocks is positioned under the ischia. Even so, if an indenter presses against muscle tissue, we should expect to get traumatized muscle. In clinical practice, skeletal muscle may become involved in serious DUs, but our experience reveals that this is mostly after the initial necrosis in connective tissues. It is also reasonable to conclude that the ulcers developing in Kosiak’s dogs were mostly in connective tissue over their femoral trochanters.

CONCLUSIONS

Why dig into all of these data? Well, we believe that some past mistakes and misunderstandings continue to confound this area of study, so that specialists in DU pathogenesis continue to hold very divergent views. Indeed, the differing and even contradictory information found in some papers defeats attempts at any reconciliation. How can clinicians develop appropriate patient care guidelines when the basics are still not clear?

REFERENCES

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1 Draelos, Z. The ability of onion extract gel to improve the cosmetic appearance of postsurgical scars. Cosmetic Dermatology, June 2008.
Cholera is a severe and often fatal secretory diarrhea caused by the bacterium *Vibrio cholerae*. Man is the only known natural host, but the organism can exist in shellfish. Transmission is through ingestion of contaminated water or food. The infectious dose varies between $10^5$ and $10^8$ organisms, with an incubation period to clinical disease from a few hours to 5 days. For each symptomatic case, there may be 5 to 40 asymptomatic or mildly symptomatic carriers that can lead to rapid spread of disease, especially when living conditions are cramped and safe water supply is inadequate.

There are no prodromal symptoms associated with cholera, and fever is unusual. The onset of diarrhea is usually abrupt and begins as mild diarrhea that rapidly gives way to passage of copious opalescent “rice-water” stool. The stool is nonodorous or has a slight fishy smell. Vomiting of fluid of similar composition may occur as a later feature.

The massive fluid loss—up to 20 L daily—leads to rapid hypovolemia, with up to 10% of a person’s body weight being lost in a few hours. Untreated, the disease is associated with a 20% to 80% mortality rate. This can be reduced to <1% with adequate rehydration.

Rapid fluid loss leads to thirst, muscle cramps, anuria, electrolyte loss, metabolic acidosis, and hypovolemic shock. Severe hypotremia and hypokalemia can result in cardiac arrhythmia and paralytic ileus. Typical “choleric facies” are presented as deeply sunken cheeks and eyes, dry skin, and dry mucous membranes.

**MICROBIOLOGY**

*V. cholerae* was first demonstrated by Koch in 1883. The species is now divided into several distinct serovars, according to their somatic (O) antigen, the most important being O1. There are two biotypes, namely classical and El Tor, the latter being first isolated from pilgrims at the El Tor quarantine station in Sinai, Egypt, in 1906.

The organism is a motile (*Vibrio* from the Latin “to move”), comma-shaped, gram-negative organism, and can be cultured on thiosulfate-citrate-bile salts-sucrose agar.

**EPIDEMIOLOGY**

The annual global disease burden of cholera is estimated to be between 3 and 5 million cases, with approximately 120,000 deaths per annum. Although eliminated as a major public health concern in developed countries, there has been no decline in incidence in developing countries, despite efforts to ensure provision of clean water and adequate sanitation.

Massive assemblies of pilgrims along the Ganges river led to 6 pandemics of cholera between 1817 and 1823. In 1961, *V. cholerae* serotype O1 El Tor emerged as the seventh pandemic and continues to spread to the present day. Symptomless carriers, who may represent 75% of those infected with the El Tor biotype, are very important in the epidemiology of this disease, as they may transport the organisms over long distances and from country to country.

In 1992, a hitherto unknown toxigenic serovar, designated O139, was identified in Madras, India and Bangladesh. The high attack rate of O139 among adults suggests that previous exposure to O1 serotype does not confer protection. This type of cholera is now spreading in the Far East, where it is replacing the El Tor serotype, raising concerns that it may lead to the eighth pandemic.

**COMMENT**

“A disease worse than death, which begins where others end, with death.”

— Magendie, Paris, 1831
HAITI CHOLERA OUTBREAK
On January 12, 2010, Haiti experienced a massive earthquake that resulted in the loss of approximately 220,000 lives and made more than 1 million people homeless. On October 20, 2010, 60 cases of acute watery diarrhea were reported at L’Hôpital de Saint Nicolas, more than 55 miles from the nearest displaced-persons camp, and were later confirmed as cholera. The outbreak has continued to spread, with almost 179,000 reported cases and 3759 reported deaths to January 7, 2011.1 Although shocking, the reported number of cases is likely to represent only a fraction of the epidemic’s true toll.

Although cholera has been present in Latin America since 1991, it has not been epidemic in Haiti for at least 100 years. Paradoxically, it now appears that the Haitian strain of the disease was imported, probably through one of the aid agencies that may have inadvertently dumped waste from their camp into a nearby river used as a source for drinking water. This strain appears to have a higher relative fitness and pathogenicity compared with previous cholera cases in the region and raises concern that this will now spread to neighboring countries.2

TREATMENT

Rehydration
Rapid rehydration with electrolyte replacement proportionate to fluid and electrolyte loss is the key to successful treatment. A rapid assessment of fluid loss can be made by collecting the watery stool in a graduated bucket placed under the large central hole in a waterproof disposable sheet upon which the patient lies.

Oral rehydration works well in all but severe cases. Oral rehydration salts to replace electrolyte loss (eg, Dioralyte) or locally prepared cereal-based formulations can dramatically reduce mortality. Luminal glucose absorption mechanism is not affected by the cholera toxin. A simple oral replacement solution can be made from 1 teaspoon of table salt and 4 heaping teaspoons of sugar added to 1 L of safe water. Intravenous fluids are indicated in persons in shock or with other signs of severe hypovolemia.

Antibiotic Therapy
Effective antibiotic therapy not only shortens the duration of excretion of V cholerae in the stool, but also shortens the duration of illness and reduces the bacterial shedding to the environment. Effective antibiotic therapy, therefore, has both individual and communal benefits that maximize the effectiveness of limited resources while optimizing patient care.

Several antimicrobials are effective in the treatment V cholerae, including doxycycline, chloramphenicol, cotrimoxazole, azithromycin, and ciprofloxacin. Administration of single-dose azithromycin has been shown to be highly effective, leading to dramatic resolution of diarrhea after 24 hours.3

If antimicrobials are to be used, this will require close monitoring for emergence of antibiotic resistance. Single plasmid-mediated resistance genes have so far been shown to spread with antibiotic pressure. The epidemic strain in Haiti is susceptible to tetracycline (a proxy for doxycycline) and azithromycin but is resistant to nalidixic acid (ciprofloxacin) and cotrimoxazole.

PREVENTION
Cholera vaccines confer only short-lived limited protection and are, therefore, not particularly effective as pre-exposure prophylaxis in outbreak management. Although they may prevent up to 50% of clinical cases, they do not lower the number of infected and therefore infectious persons. Vaccination is, therefore, likely to lead to a false sense of security both among vaccinees and the authorities. Contacts with patients with proven disease, however, should receive vaccine as post-exposure prophylaxis. All faeces and bed linen of patients with known cases should be destroyed. Toxoid vaccines using inactivated toxin have so far been shown to be ineffective.

As our understanding of the pathophysiology of cholera improves, it is anticipated that the efficacy of newer cholera vaccines will increase. The challenge is the emergence of more virulent and antibiotic-resistant strains of cholera such as those that are appearing in Bangladesh and have now appeared in Haiti.

Breaking the link between safe drinking water and sewerage remains the key to prevention and control, as it was when Dr John Snow identified the Broad Street pump as the source of the Soho outbreak in London in 1854. This epidemic was immediately halted when the pump handle was removed.4 As an increasingly interconnected global population surpasses 7 billion, the potential for further cholera outbreaks and pandemics will increase. A “good Samaritan” stockpile of cholera vaccine for rapid deployment to countries in need has been proposed as a lever in “vaccine” diplomacy.5

FIVE BASIC CHOLERA PREVENTION MESSAGES
1. Drink and use safe water: piped water sources, drinks sold in cups or bags, or ice may not be safe and should be boiled or treated with chlorine.
2. Wash your hands often with soap and water: if no soap is available, scrub hands often with ash or sand and rinse with safe water.
3. Use latrines or bury your feces; do not defecate in any body of water.


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4. Cook food well, keep it covered, eat it hot, and peel fruit and vegetables ("boil it, cook it, peel it, or forget it").
5. Clean up safely—in the kitchen and in places where the family bathes and washes clothes.

REFERENCES

BIBLIOGRAPHY

HISTORICAL DIAGNOSIS & TREATMENT
Diagnosis and treatments have advanced over the past century. This feature depicts conditions from a collection of stereopticon cards published in 1910 by The Stereoscopic Skin Clinic, by Dr. S. I. Rainforth.
Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphomas (CTCLs), representing 44% of newly diagnosed primary cutaneous lymphomas in the Dutch experience, 82% at three academic dermatology departments in the United States, and 72% in a multicenter study conducted in Argentina.1–3

As first described by Alibert and Bazin in the 19th century, clinical-pathologic manifestations of MF include multiple patches and plaques that may progress to tumors. The classical Alibert-Bazin disease (cMF) is now recognized as an indolent cutaneous lymphoma with three well-defined variants: follicular MF, pagetoid reticulosis, and granulomatous slack skin.

Many variants of this lymphoma differ substantially from cMF, and are, therefore, sometimes referred to as atypical or unusual forms of MF, most of which resemble other dermatologic diseases.4,5

The objective of this investigation was to evaluate the prevalence of infrequent variants of MF among patients with a diagnosis of MF and to estimate the clinical course in relation to their stage at the time of diagnosis, disease progression, and response to initial treatment. This was an observational, descriptive, retrospective cohort analysis. Between November 1995 and June 2010, all patients with a clinicopathologic and immunophenotypic diagnosis of CTCL (World Health Organization/European Organization for Research and Treatment of Cancer, 2005) seen in our department were included in a database. Follow-up data were collected yearly. The following variables were recorded: sex, age, date of definitive diagnosis, stage, type, response to initial treatment, and disease course.

Among 135 patients with primary cutaneous lymphomas, 130 had CTCL. Of the latter, 98 (75.38%) had MF (56 men). The mean age at diagnosis was 51.97 years (range, 12–77 years). From the group of MF patients, 32 (32.65%) had atypical variants (20 men), with a mean age of 44.91 years (range, 12–76 years). These cases included 10 follicular MF, 6 hypopigmented MF, 5 poiquilodermic MF, 4 erythrodermic MF, 3 unilesional MF, and 1 case each of granulomatous slack skin, ichthyosiform MF, pigmented purpura-like MF, and bullosa MF (Figure 1).

Staging evaluation of these atypical variants revealed that 15 (47%) were at an advanced stage (IIB to IV), while 17 (53%) were at stage IA to IIA at the time of diagnosis. We evaluated response to therapy and found that 15 patients (47%) achieved complete response to initial treatment and 12 patients (37%) achieved partial response. The analysis of the group with complete response revealed that 5 patients (33.3%) were treated with psoralen–UV-A (PUVA) and low doses of interferon (IFN) α, and 5 (33.3%) were treated with sun irradiation and topical corticosteroids. The remaining 5 patients were taking IFN combined with total skin electron beam therapy, retinoids with PUVA, sun exposure associated with topical corticosteroids.
Unusual Variants of Mycosis Fungoides

and thalidomide, and topical corticosteroids alone. The disease course was mild for most variants and disease progression was followed-up in 4 patients with FMF: 1 patient had visceral involvement and death related to the disease, 1 had rapid progressive-stage disease followed by death, and 2 had transformation to large-cell lymphoma. Another patient with BMF showed rapid cutaneous spread also with transformation to an anaplastic large T-cell lymphoma followed by death 22 months after diagnosis. One of the patients with EMF showed a positive lymph node. The mean follow-up period after diagnosis of lymphoma was 37.49 months (range, 3–128 months).

DISCUSSION

In a previous report, we found 17 cases until August 2007. During the later years we could identify 15 cases, allowing us to infer that unusual variants of MF are more frequent than we expected or that an accurate grade of suspicion at the time of diagnosis was developed.

FMF was the most frequent variant of MF, representing 31.25%. Clinical features in FMF are hair loss in the affected area, hyperkeratotic follicular papules, and cyst-like lesions (Figure 2). The face, neck, and trunk are the most commonly affected areas, and there is a significantly higher male to female ratio. All cases were consistent with these features. Dense folliculocentric infiltrates are the histopathologic hallmark in FMF (Figure 3). Cells are small to medium and mucin deposition is common. While 4 patients with this variant had a poor clinical course, the other 6 patients had stable disease with good response to initial treatment, although sustained remission could not be achieved.

To define EMF, a previous history of cMF is required, together with absent or minimum blood involvement. The 4 patients in this series were men. We could observe a progressive disease state with lymph node spread in one of them.

Clinical features in PMF include hypopigmentation or hyperpigmentation, dryness, skin atrophy, and telangiectasias. Histopathologic examination shows atrophy of the epidermis, vacuolar alteration of the basal layer, melanophages, and dilatation of superficial blood vessels. There were 5 patients (15.62%) with a diagnosis of PMF in our group, and 4 were men. All patients had a stable disease with very good response to initial treatment (in most of cases, sun exposure plus topical corticosteroids) and sustained remission.

A total of 6 patients (18.75%) from the group of atypical MF had a diagnosis of HMF. Mean age of this group was 26.07 years. The youngest 5 patients were aged between 12 and 28 years, and hypopigmentation was the only feature of the disease (Figure 4). The remaining patient, a man aged 68, developed this unusual variant after cMF and had an advanced stage at diagnosis. Classical features of MF can be seen in the histopathology. There are no histopathologic markers for this type. This variant affected patients at a younger age, most of whom had stable disease with a good response to treatment, but recurrences were frequent.

Unilesional MF is defined by single typical MF lesions, or lesions limited to an isolated individual area involving <5% of the body surface. The breasts, axilla, and buttocks are the most commonly
affected areas. There were a total of 3 patients (9.37%) with UMF in our study, all of whom were women who had very good response to topical corticosteroids.

Granulomatous slack skin (GSS) occurs most frequently in flexural areas in women. There is a high association with Hodgkin disease. It is characterized by slowly developing bulky, infiltrated folds of atrophic skin in flexural areas. Apart from the epidermotropic infiltrates, the specific finding is the presence of a granuloma with multinucleated giant cells containing lymphocytes and elastic fibers in their cytoplasm. Elastic fibers are almost totally absent. We had only one patient with GSS, a 44-year-old woman with a previous history of patch-stage cMF but with a fluctuating course and a poor response to treatment until she developed this variant (Figure 5).

Vesiculobullous lesions are an extremely rare manifestation of MF. Kaposi reported the first case of BMF in 1887 and described it as pemphigus-like MF. BMF commonly presents in elderly patients (with an average age of approximately 66 years) and has no sex predominance. Blisters can superimpose on typical skin lesions of classic MF and Sézary syndrome. The trunk and limbs are predominantly affected. Bullous lesions usually appear months to years after classic MF patches and plaques, but, in some cases, they are present as the primary manifestation. The presence of epidermotropism and cerebriform atypical lymphocytes in microscopic studies of the bullous tissue samples, are the cardinal guide to the diagnosis of BMF. Blisters can be seen in different locations on the skin, including subcorneal, intraepithelial, and subepidermal. Immunofluorescence studies are negative. Other bullous diseases must be excluded before the diagnosis of BMF can be established.

BMF represents a particularly aggressive form of MF and is associated with a poor prognosis. Only 1 patient (3.12%) in our series had BMF. The patient was a man with classical clinical features (Figure 6). We performed multiple biopsies, all with an unspecific histopathology until reaching a definitive diagnosis. Later, he underwent rapid transformation to an anaplastic large cell lymphoma CD30+ and died 22 months after diagnosis, during chemotherapy, due to sepsis.

In IMF, we find widespread ichthyosiform lesions, comedo-like lesions, and or follicular keratotic papules, most frequently seen on the extremities. Pruritus is the rule. One patient (3.12%) in our series had IMF, a 65 year-old man with a 4-year history of xeroderma and pruritus until a final diagnosis of MF was made (Figure 7). Complete and sustained remission was achieved with PUVA and IFN-α.
It is important to rule out purpuric drug eruptions in association with PPMF, which can be monoclonal, and therefore a close follow-up is required.4,5

CONCLUSIONS
Among 98 patients with MF, 32 were unusual variants, with FMF, EMF, PMF, and HMF being the most frequent types. As in the classical disease, we found a male predominance (62.5%) but at a younger age. The youngest patients were those with HMF. Most variants had an indolent course. Recurrence was common in HMF.

A total of 47% were at an advanced stage, probably because of the 10 patients with FMF who were considered to have tumor-stage disease, regardless of their clinical appearance, as it has been proposed by the Dutch group. Another 47% achieved complete response after initial treatment. Among complete responders, 33.3% were treated with PUVA and low doses of IFN-α and 33.3% with sun irradiation and topical corticosteroids.

Although there was good response to initial treatment in FMF, most patients could not achieve sustained complete remission. Disease progression and MF-related death were almost entirely restricted to FMF, BMF, and EMF. There is a wide range of clinical presentations in MF. It is important to recognize these unusual variants of MF, because misdiagnosis in the early stages could delay the correct diagnosis and prompt treatment with prognostic and therapeutic implications.

REFERENCES
HISTORICAL DIAGNOSIS & TREATMENT: SARCOMA (continued from page 217)

Sarcomas are malignant connective tissue tumors which may have their origin in any organ of the body and are only occasionally primary, but not infrequently secondary, in the skin. They may be classified as non-pigmented and melanotic. There is little difference in the clinical course of the two except that the melanotic form is much more malignant. A sarcoma may arise in the skin without any visible antecedent lesion, but more often it develops from a nevus, especially from one that has been irritated by trauma, cauterization or electrolysis. When the original nevus is pigmented the malignant growth is apt to reproduce the pigment but not necessarily in the same degree. Melanotic sarcomas vary in color from grayish brown to bluish black. The skin over a non-pigmented sarcomatous node may be normal in color but is often reddish or purplish on account of its increased vascularity. A nevus that has undergone malignant transformation first gives evidence of the fact, as a rule, by an increase in size or change of color. About a pigmented mole a dark areola may spread out, or clusters of black puncta develop in close proximity. Occasionally without noticeable change in the mole there occurs a swelling of adjacent lymph glands which on microscopic examination may be found to contain groups of tumor cells similar to those of the original growth. A melanotic sarcoma sometimes develops primarily in a nail fold and has the appearance of a chronic paronychia with pigmented spots suggestive of silver nitrate stains. Sarcomatous tumors occasionally, though rarely, attain the size of an orange. They are usually sessile and hemispheroideal or lobulated and may be firm and elastic or somewhat doughy and compressible. They are at times slightly tender. Some non-pigmented growths are very much more slow to spread by metastasis than the melanotic tumors, and being less malignant are more apt to reach a large size. Sarcomas are always quite vascular and therefore when not situated in a region in which they are particularly exposed to trauma are little inclined to ulcerate. But over a large tumor the epidermis in time becomes thinned and abraded and a granulated vascular surface is exposed. The skin about the tumor may be diffusely infiltrated and discolored. By the time a growth has reached this stage there are usually numerous metastatic tumors in the skin and viscera. Sarcomatosis cutis or generalized sarcoma of the skin may arise thus from a primary cutaneous growth, but is more often secondary to disease of a deeper organ. Multiple melanotic growths spring not infrequently from a sarcoma of the choroid, as in the case illustrated, in which there was exopthalmia on the right due to the presence of the tumor in the orbit. Nodes develop in various regions but rarely reach any considerable size because death soon ensues. The duration of life may be many years from the onset of the least malignant non-pigmented form, but with the melanotic variety it rarely exceeds three years and may be only four or five months. The disease may occur at any age.

TREATMENT: Excision of a slow growing non-pigmented primary growth may be curative, but nothing short of early amputation of the limb on which a melanotic sarcoma has started will prevent its becoming generalized. Multiple growths of both kinds are hopeless, although cures have been reported from the hypodermic administration of arsenic, and from injections of the combined toxins of Streptococcus pyogenes and B. prodigiosus.
Important Safety Information for DUAC Topical Gel

- DUAC Topical Gel is contraindicated in patients who have shown hypersensitivity to any of its components or lincomycin
- DUAC Topical Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis
- Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus
- For dermatologic use only; not for ophthalmic use
- Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents
- The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures
- Clindamycin- and erythromycin-containing products should not be used in combination. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vivo antagonism is not known
- DUAC Topical Gel may bleach hair and colored fabrics
- Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn
- DUAC Topical Gel should be given to a pregnant woman only if clearly needed
- It is not known whether DUAC Topical Gel is secreted into human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother
- Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established
- Adverse reactions may include erythema, peeling, burning, and dryness
- Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in postmarketing use with DUAC Topical Gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure

Please see brief summary of Prescribing Information on following page.

References:
**DUAC® Topical Gel**

clindamycin, 1% - benzoyl peroxide, 5%)

The following is a brief summary only; see full prescribing information for complete product information.

**For Dermatological Use Only.**

Not for Ophthalmic Use. Rx Only

**INDICATIONS AND USAGE**

DUAC Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris. DUAC Topical Gel has not been demonstrated to have any additional benefit when compared to benzoyl peroxide alone in the same vehicle when used for the treatment of non-inflammatory acne.

**CONTRAINDICATIONS**

DUAC Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis.

**WARNINGS**

**ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBiotic FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY Clostridium difficile IS ONE PRIMARY CAUSE OF ANTIBIOTIC-ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERSISTENT DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR Clostridium difficile AND STOOL ASSAY FOR Clostridium difficile TOXIN MAY BE HELPFUL. SYSTEMATICALLY WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ENSURE A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIPEPTOSTREPTOCOCCAL AGENTS SUCH AS OXPATINE AND DIPHENOXYLATE WITH ATROPINE MAY PROLONG AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSATION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

**PRECAUTIONS**

**General:** For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. The use of antibacterial agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures. Avoid contact with eyes and mucous membranes. Clindamycin and erythromycin containing products should not be used in combination. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in *vivo* antagonism is not known.

**Information for Patients:** Patients using DUAC Topical Gel should receive the following information and instructions:

1. DUAC Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.

2. This medication should not be used for any disorder other than that for which it was prescribed.

3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.

4. Patients should report any signs of local adverse reactions to their physician. Patients who develop allergic symptoms such as severe swelling or shortness of breath should discontinue use and contact their physician immediately.

5. DUAC Topical Gel may bleach hair or colored fabric.

6. DUAC Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children. Discard any unused product after 2 months.

7. Before applying DUAC Topical Gel to affected areas, wash the skin gently with warm water, and pat dry.

8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced squamous cell skin tumors in transgenic Tg.AC mice in a study using 20 weeks of topical treatment. The clinical significance of this is unknown.

In a 2-year dermal carcinogenicity study in mice, treatment with DUAC Topical Gel at doses up to 8000 mg/kg/day (16 times the highest recommended adult human dose of 2.5 g DUAC Topical Gel, based on mg/m²) did not cause an increase in skin tumors. However, topical treatment with another formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, or 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats.

In a 52-week photo carcinogenicity study in hairless mice (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical treatment with DUAC Topical Gel and exposure to ultraviolet radiation.

Genotoxicity studies were not conducted with DUAC Topical Gel. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Studies have not been performed with DUAC Topical Gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g DUAC Topical Gel, based on mg/m²) revealed no effects on fertility or mating ability.

**Pregnancy: Teratogenic Effects:** Pregnancy Category C: Animal reproduction studies have not been conducted with DUAC Topical Gel or benzoyl peroxide. It is also not known whether DUAC Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. DUAC Topical Gel should be given to a pregnant woman only if clearly needed.

Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) revealed no evidence of teratogenicity.

**Nursing Women:** It is not known whether DUAC Topical Gel is secreted into human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

**ADVERSE REACTIONS**

During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment were as follows:

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<th>Combined results from 5 studies (n = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Treatment (Baseline)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
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<tr>
<td>Erythema</td>
<td>28%</td>
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<tr>
<td>Peeling</td>
<td>6%</td>
</tr>
<tr>
<td>Burning</td>
<td>3%</td>
</tr>
<tr>
<td>Dryness</td>
<td>6%</td>
</tr>
</tbody>
</table>

(Percentages derived by # subjects with symptom score/# enrolled DUAC Topical Gel subjects, n = 397).

Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in post-marketing use with DUAC Topical Gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relation to drug exposure.

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evolved in the 1950s, vancomycin is a glycopeptide antibiotic that inhibits peptidoglycan biosynthesis within the bacterial cell wall. Vancomycin has the distinct advantage of having activity against β-lactam–resistant bacteria. Since then, its use has increased as a result of the increase in the incidence of methicillin-resistant Staphylococcus aureus (MRSA) infections. In the United States today, 58% of S. aureus isolates are methicillin resistant. In addition, the mortality associated with MRSA infections is greater than that associated with methicillin-sensitive S. aureus infections. Even though increasing numbers of vancomycin-resistant cases have been documented, vancomycin remains the antibiotic of choice in the hospital setting when a MRSA infection is suspected or has been diagnosed in patients who do not have severe renal impairment. Here, we present 5 cases of vancomycin-induced eruptions to highlight the many skin reactions to this antibiotic, some of which can be serious or fatal. In reporting these reactions, we hope to place vancomycin in the differential diagnosis of these eruptions in patients who have received this medication.

REPORT OF CASES

We reviewed the clinical information for 5 patients with apparent vancomycin sensitivity. The Table presents the patient information and the histopathologic findings.

CASE 1

A 45-year-old African American man with a medical history significant for end-stage renal failure, end-stage liver disease, hepatitis B virus infection, and human immunodeficiency virus (HIV) infection was treated with vancomycin for Clostridium difficile colitis. After 2 days of treatment, the patient developed a blistering, exfoliative eruption on his arms and legs (Figure 1). Linear immunoglobulin A (IgA) bullous dermatosis was clinically suspected. The eruption subsided after vancomycin therapy was discontinued and camphorylated moisturizing lotion was applied.

CASE 2

A 54-year-old white woman was initially admitted for an intracerebral hemorrhage. Her hospital course was complicated by fever, leukocytosis, and aspiration pneumonia, prompting treatment with vancomycin. After treatment, the patient developed an eruption on the neck and body that became more severe over time, causing edematous, dusky red plaques studded with pustules on the trunk and extremities (Figure 2). Discontinuation of vancomycin resulted in amelioration of the eruption.

CASE 3

A 46-year-old African American woman with chronic stage II renal failure was admitted for worsening edema and shortness of breath. The patient subsequently developed respiratory failure and vancomycin was started. Within a few days, the patient exhibited expansive purpura on her abdomen, groin, thighs, and left breast, which also had areas of denuded skin (Figure 3). Epidermal sloughing, erosions, and blisters covered more than 40% of her body surface area. The patient also had a positive Nikolsky sign. A biopsy specimen from the left breast showed focal subepidermal bullae formation with patchy, mild, perivascular, inflammatory cell infiltrate. Discontinuation of vancomycin and
treatment of denuded skin with petroleum jelly–impregnated gauze was prescribed. Unfortunately, the patient was terminally ill and died.

**CASE 4**

An 84-year-old white man who had an anterior myocardial infarction and rhabdomyolysis was admitted to the hospital. The patient was intubated 2 weeks after admission secondary to respiratory failure, and vancomycin and piperacillin–tazobactam were subsequently started. By day 2 of antibiotic treatment, the patient developed a blanchable, pink, morbilliform eruption on his arms, trunk, and legs (Figure 4). Papules also formed that coalesced into plaques in his groin. Discontinuation of vancomycin and application of topical steroids alleviated the reaction.

**CASE 5**

An 18-year-old white woman with a medical history of Arnold-Chiari syndrome who had a shunt placed was initially started on cefepime. Vancomycin was added 1 week later. Approximately 11 days after the start of vancomycin therapy, the patient presented with fever and lymphadenopathy. Shortly thereafter, she developed a diffuse eruption of bright pink-red, excoriated papules that coalesced into large plaques (Figure 5). This eruption affected the entire body, sparing only the face. Erythroderma was diagnosed. The eruption improved with the discontinuation of vancomycin, application of topical steroids, and administration of antihistamine.

**DISCUSSION**

Adverse drug reactions are a major cause of morbidity and mortality around the world. Adverse events to medications have been reported to occur in nearly 30% of hospitalized patients, and even more astounding is the finding that up to 28% of hospital admissions are associated with adverse drug eruptions. A variety of adverse reactions to vancomycin have been reported that affect multiple organ systems. Rapid infusion of the drug has been documented to cause side effects such as nausea, colitis, interstitial...
nephritis, renal failure, hematologic reactions, ototoxicity, and thrombophlebitis. Vancomycin-induced drug reactions specific to the skin include exfoliative dermatitis, toxic epidermal necrolysis, hypersensitivity reactions, linear IgA bullous dermatosis (LABD), and “red man syndrome.”

LABD, a rare blistering disease, has been well documented to occur in association with intravenous vancomycin administration. LABD is a disease of subepidermal blistering due to the deposition of IgA in a linear array at the dermal-epidermal interface. Immunofluorescence shows a characteristic linear pattern of IgA deposition along the basement membrane zone.

A subgroup of LABD cases are known to be drug-induced. Although numerous medications have been associated with LABD including diclofenac, captopril, and phenytoin, intravenous vancomycin is the most well-documented drug to cause this reaction. Interestingly, on rechallenge, the reaction will have a shorter time to presentation and a longer total course. Other studies have indicated that a vancomycin-induced LABD response is not dose-dependent and may be due to an autoantibody to BP120 and LAD285.

Acute generalized exanthematous pustulosis (AGEP) is a well-known adverse cutaneous drug reaction consisting of numerous small sterile pustules against a background of edema and erythema that usually begins on the face or around large skin folds. Systemically, this cutaneous eruption is associated with fever and leukocytosis.

The incidence of AGEP has been approximated at 1 to 5 cases per million annually. An analysis of 63 cases of AGEP showed that drugs (β-lactam and macrolide antibiotics most frequently) were the cause in 87%; other causes included viral infections, UV radiation, and mercury poisoning. AGEP secondary to drugs may take 1 to 3 weeks to become visible after new drug administration, but latency periods can decrease to only 2 to 3 days on rechallenge.

Toxic epidermal necrolysis (TEN) is an eruption of the skin that usually begins as very tender, pink-red patches, plaques, or target-like macules that subsequently evolve into full-thickness necrosis of the epidermis. The epidermis then peels off in sheets. On physical examination, the Nikolsky sign, bulla formation, and expansive areas of denuded skin may be observed. Medications are often cited as the most likely cause of this reaction. Drugs with a high risk of causing epidermal necrolysis include allopurinol, sulfamethoxazole, carbamazepine, lamotrigine, and phenytoin. Although few reports of vancomycin-induced TEN have been documented, we believe that vancomycin treatment should be considered as a possible cause in patients presenting with epidermal necrolytic reactions. The literature includes reports of patients in renal failure treated with vancomycin who develop TEN reactions, just as in the case we describe here. Vancomycin-induced TEN has also been seen in patients with HIV infection. Interestingly, cases of vancomycin-induced LABD mistaken as TEN reactions have also been documented. Morbilliform eruptions of the skin, so named to describe their similarity in appearance to the viral exanthem of measles, represent the most commonly encountered cutaneous drug reaction. Clinically, these eruptions manifest as pink maculopapular

Figure 2. Edematous red plaques studded with pustules can be seen on this patient’s right lateral arm.

Figure 3. Epidermal sloughing and large erosions can be seen on this patient’s trunk.
rashes on the trunk 1 day to 4 weeks after initiation of treatment. Within hours, this eruption can spread to involve the face and extremities, although it usually spares the mucous membranes and acral surfaces.17

Classically, ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole cause this reaction. Vancomycin has recently been shown to cause a morbilliform variant of LABD in which deposition of IgA at the dermoepidermal junction is present but bullae are not formed.18 Reports of systemic absorption of oral vancomycin resulting in maculopapular eruptions have been published as well, supporting the notion that oral vancomycin can occasionally reach therapeutic systemic levels.19,20

Erythroderma can be described as diffuse erythema and scaling of more than 90% of the skin’s surface area. Systemic physical findings such as fever, tachycardia, peripheral edema, and generalized lymphadenopathy are often present as well.21 Medication classes well known to cause this type of reaction include antibiotics, antiepileptic agents, and calcium channel blockers. Vancomycin-induced erythroderma has been reported in patients with renal compromise, often causing prolongation of the reaction because the patient’s ability to clear the drug from the body is inhibited.22–24 Vancomycin-induced erythroderma can be readily distinguished from the “red man syndrome” because the latter is an infusion reaction.24

We have reported here the cases of 5 patients with cutaneous reactions to vancomycin treatment. Our purpose in reporting these cases is to increase awareness and aid in the diagnosis of cutaneous manifestations attributable to vancomycin. Use of vancomycin, a drug best known for treating invasive *S aureus* infections in hospitalized patients, has become more widespread.
with the rise of methicillin resistance. Clinicians should keep this medication in mind as a cause of cutaneous eruptions, especially when evaluating hospitalized patients who have recently started vancomycin treatment.

Acknowledgement: Presented at the 2010 Spring meeting of the Section on Dermatology of the College of Physicians of Philadelphia.

REFERENCES

Available soon...

A New Tretinoin Therapy
From Triax Pharmaceuticals
Mobile Teledermatology: As Doctors and Patients Are Increasingly Mobile, Technology Keeps Us Connected

Dina Farshidi, BA; Noah Craft, MD, PhD, DTM&H; Maria Teresa Ochoa, MD

ABSTRACT

With advancements in electronics and health informatics, telemedicine has emerged as a cost-effective tool capable of increasing care to remote regions, facilitating specialist consultations, supporting self-management by patients, and sharing knowledge over great distances. In this review, the authors discuss existing telemedicine modalities, highlight examples of mobile systems documented in the literature to date, and emphasize the data supporting the feasibility of telecommunication technologies to deliver dermatology services and education remotely. While many studies have suggested the potential for teledermatology to increase access to care in developing countries with few dermatologists, the authors share some of the most recent developments, including the use of diagnostic decision support software. The authors encourage a thriving and open network that will enhance the ongoing research and development of innovative and useful products. This network will also connect dermatologists willing to volunteer their consultation to health care workers in remote areas lacking specialists.

(SKINmed. 2011;9:231–238)

The collision of electronics and information technology within the field of medicine has resulted in the revolution we call eHealth. Telemedicine is one manifestation of eHealth with the potential to increase care to remote regions, to facilitate specialist consultations, to support self-management by patients, and to share knowledge over great distances. These advances may greatly benefit patient care, medical education, and postgraduate training in cost-effective ways. Today, telemedicine may be as simple as two health care professionals discussing a case over the telephone or as complex as using satellite technology and videoconferencing equipment to conduct real-time consultations between medical specialists in two different countries. Most recently, the soldiers in the eHealth revolution have left their examination rooms and their offices to become completely mobile (Table I). This practice is loosely called mHealth, for Mobile Health.

TELEDERMATOLOGY: ITS EVOLUTION AND CLASSIFICATION

Despite reports of dermatologists evaluating employees at Boston’s Logan Airport through a live black-and-white video link in 1972, the term teledermatology (TD) was not coined until 1995. Since then, a plethora of different modalities have been developed (Table II). Early TD was classified as either synchronous or asynchronous. Synchronous TD refers to videoconferencing between two doctors with a patient at the remote site. Asynchronous refers to “store-and-forward” technology where one health care provider captures a digital image of a patient at a remote site and sends it electronically to a specialist. The specialist can review the consultation request at a convenient location and time. Most recently, TD has been more broadly categorized based on technology tools, the health care professionals involved, and special areas of TD application.

MOBILE TD: FROM TEXT MESSAGES TO DERMATOSCOPES

One technology included in modern classification schemes is mobile TD (MTD). MTD is defined as the use of portable devices, such as mobile phones with built-in cameras, to capture, compute, and share information through wireless networks. Depending on the sophistication of the mobile device, MTD can serve a variety of purposes.
### Table I. Existing Examples of Mobile Telemedicine

<table>
<thead>
<tr>
<th>DISCIPLINE</th>
<th>PURPOSE</th>
<th>SOFTWARE</th>
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</thead>
<tbody>
<tr>
<td>Medicine (cardiology, endocrine)(^{37})</td>
<td>Self-care for diabetes and cardiovascular disease</td>
<td>MediNet software: makes personalized recommendations to patients based on readings from monitoring devices and information known about the patient</td>
</tr>
<tr>
<td>Medicine (cardiology)(^{38})</td>
<td>Out-of-hospital follow-up of cardiac patients</td>
<td>Portable recording software: supports data transmission via mobile smart phones</td>
</tr>
<tr>
<td>Medicine (cardiology)(^{39})</td>
<td>Remote electrocardiographic (ECG) monitoring</td>
<td>Recording system: records and transmits ECG data via mobile smart phones</td>
</tr>
<tr>
<td>Medicine (cardiology)(^{40})</td>
<td>Monitoring patient ECG and movement during daily activities</td>
<td>Java-based system: includes chest electrode and recording system connected to mobile phone</td>
</tr>
<tr>
<td>Medicine (endocrine)(^{41})</td>
<td>Self-management for type 2 diabetes</td>
<td>Few touch application: includes off-the-shelf blood glucose meter, tailor-made step counter, and food habits recorder and offers user feedback and guidance</td>
</tr>
<tr>
<td>Medicine (endocrine)(^{42})</td>
<td>Intensive self-insulin therapy</td>
<td>Intelligent neural network: indicates how much insulin to inject in accordance with lifestyle and individual glucose level inputs</td>
</tr>
<tr>
<td>Medicine (endocrine)(^{43})</td>
<td>Self-management of type 1 diabetes</td>
<td>Real-time teledermatology: based around transmission and feedback of data to and from a mobile phone</td>
</tr>
<tr>
<td>Medicine (intensive care)(^{44})</td>
<td>Remote monitoring system to support telediagnosis for intensive/critical care unit patients</td>
<td>Mobile remote monitoring system: includes real-time waveform monitoring, list trend monitoring, graph trend monitoring, and patient information checking</td>
</tr>
<tr>
<td>Medicine(^{45})</td>
<td>Remote patient monitor</td>
<td>MIMOSA architecture and open development platform: includes ambient intelligence applications (ie, ECG acquisition and glucose level monitoring)</td>
</tr>
<tr>
<td>Medicine(^{46})</td>
<td>Remote monitoring and management of chronic disease</td>
<td>MOTOHEALTH mobile health care solution: connectivity interface based on the HL7 standards</td>
</tr>
<tr>
<td>Medicine(^{47})</td>
<td>Remote patient monitoring and data retrieval</td>
<td>Store-and-forward software: transfers patient information</td>
</tr>
<tr>
<td>Medicine(^{48})</td>
<td>Medical professional educational assistance</td>
<td>Medical decision support system: collects, analyzes, and distributes diagnostic information</td>
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<tr>
<td>Medicine (geriatrics)(^{49})</td>
<td>Home support</td>
<td>Case report creation support system: allows for case creation and communication through mobile phones</td>
</tr>
<tr>
<td>Medicine (geriatrics)(^{50})</td>
<td>Safety support to assist in the care of elderly patients</td>
<td>Safety support system: identifies patient location via mobile phone</td>
</tr>
<tr>
<td>Medicine (geriatrics)(^{51})</td>
<td>Home health requests by patients</td>
<td>Home welfare and care services support system: allows patients to use a pen-type image sensor to request products and services</td>
</tr>
<tr>
<td>Medicine (geriatrics)(^{52})</td>
<td>Monitoring mobility trends of elderly patients</td>
<td>Custom-designed mobility alert software: monitors and records patient mobility via mobile phone</td>
</tr>
<tr>
<td>Medicine (home health)(^{53})</td>
<td>Around the clock communication between patients and contact center personnel</td>
<td>Citizen health system: modules allow for communication between the patient and the contact center using mobile phone</td>
</tr>
<tr>
<td>Medicine (preventive medicine)(^{54})</td>
<td>Self-monitoring health behaviors interventions</td>
<td>Mobile diary and support system: records and monitors health-related self-observations and offers solutions to patient via mobile phone</td>
</tr>
<tr>
<td>Medicine (oncology)(^{55})</td>
<td>Symptom and quality-of-life monitoring</td>
<td>Wireless health outcomes monitoring system: allows communication between patient and provider via mobile phone</td>
</tr>
<tr>
<td>Medicine (hematology and infectious disease)(^{56})</td>
<td>Bacillus counting for diagnostic purposes</td>
<td>Microscopy system with image analysis software: capable of brightfield and fluorescence imaging and automating bacillus counting</td>
</tr>
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</table>

*SKINmed. 2011;9:231–238*
Dermatology\textsuperscript{57} & Self-management for psoriasis patients & Teledermal management system: allows patients to share health parameters, take photos of lesions, and report adverse effects with physician who can respond with feedback

Obstetrics/gynecology (endocrine)\textsuperscript{58} & Intensive insulin treatment of pregnant type 1 diabetic out-clinic patients & Telematic system: consists of a patient teletransmission module with one-box blood glucose meter and electronic logbook and a central clinical control unit with DIAPRET (insulin monitor)

Obstetrics/gynecology (oncology)\textsuperscript{59} & Cervical cancer screening & Telemedical system: remote doctor sends clinical images of cervix with mobile phone in conjunction human papilloma virus results to central gynecologist

Emergency medicine (trauma)\textsuperscript{60} & Teleconsultation for trauma patients presenting to the emergency department & Teltrauma system: simultaneous transmission of a patient’s video, medical images, and ECG signals

Surgery (orthopedics)\textsuperscript{61} & Remote radiology consultation for orthopedic trauma patients & Telediagnosis system: includes sending station, transmission network, storage device, viewing station, and software package

Neurology/radiology\textsuperscript{62} & Teleconsultation for patients with suspected stroke & Toolbar software: transmits emergency information including head computer tomography via mobile phone

Neurology/radiology\textsuperscript{63} & Remote teleradiology consultation for brain trauma patients & Wireless system: sends images to personal digital assistant

In its simplest form, mobile phone text messages have been used in dermatology to encourage preventative health measures. As one example, in a 6-week randomized, controlled trial, the use of daily text messages detailing local weather information and suggesting sunscreen application significantly increased sunscreen application.\textsuperscript{5}

For more advanced uses, several feasibility studies using MTD have been conducted. Because clinical visual observation is the gold standard for many dermatologic diagnoses, dermatology is arguably the most suitable specialty for the use of information and telecommunication technologies to deliver services from a distance. In one early study, the concordance of diagnoses of dermatologic conditions using digital images, live examinations, and skin biopsies were compared and showed the use of digital images to be accurate and reliable.\textsuperscript{4}

As with many nascent technologies, early studies must not be accepted as static facts since more recent technologic advances may have already overcome some of the limitations identified by these studies. For example, early pilot studies suggested that low image quality was a major limitation; however, the usability and feasibility of MTD improved along with the optics and macro-imaging capabilities of inbuilt cameras. Examples of images sent from recent applications are shown in Figure 1. Various studies have demonstrated a concordance of 70% to 94% between the opinions of teledermatologists and face-to-face dermatologists.\textsuperscript{5, 6, 8}

In Figure 1, Examples of images sent using the Nexus One phone and ClickDerm software (A–C). Example of a clinical image sent using a commercial camera and store-and-forward e-mail-based software (D).

<table>
<thead>
<tr>
<th>Table II. Classification of Teledermatology</th>
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<tr>
<td>Synchronous</td>
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<tr>
<td>Asynchronous</td>
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\textit{SKINmed}. 2011;9:231–238 233 Mobile Teledermatology
These early studies demonstrated that TD is very feasible, and support the notion that the technology could be useful for off-site dermatologic consultations.

Another example of MTD utility is the mobile phone–based telemedicine compliance management system for patients with psoriasis.11 Using mobile phones with inbuilt 3.2-megapixel cameras, patients were prompted to answer questions relative to their history and take photos of their psoriasis lesions. Size and color reference markers were included close to their skin lesions to help standardize the photography. The data were then automatically sent to the patient’s physician who could easily track the evolution of the lesion via a Web browser and send feedback to the patient through a dedicated messaging system. In case of an adverse event, a Short Message Service (SMS) or e-mail alert was sent to the dermatologist to expedite action. From the physician’s point of view, this application simplifies the patient-physician communication, shortens the mean duration of regular outpatient follow-up, and facilitates individual therapy adjustment based on the availability of photos from all lesions at regular intervals. For patients, this application empowers them to become increasingly involved in their own care.

A similar patient-driven mobile home monitoring system for patients with moderate to severe psoriasis was recently developed and tested.12 There was a 71% to 98% correlation between the face-to-face physicians and teledermatologists. Differences were attributed mainly to an inability to see the entire body and, therefore, estimate total body involvement, as well as to palpate lesions and thus estimate the induration of lesions.

To provide images with greater detail and thus more clinical information, several groups have also introduced the practice of teledermatoscopy. This approach enables the electronic transfer of images captured with mobile phones coupled with a pocket dermatoscope. Because teledermatoscopy is most useful for the evaluation of pigmented lesions, most research has focused on using teledermatoscopy as a triaging or screening tool. In one study, there was a 91% concordance rate between face-to-face and teledermatoscopic diagnosis of pigmented skin tumors.11 Others found a diagnostic accuracy of 83% for teledermatoscopy compared with conventional histopathologic diagnosis.12 Regarding management decisions, there was also significant agreement between clinic-based dermatologists and remote teledermatologists regarding the diagnosis and management of pigmented lesions ($k$=0.68–0.92).13,14 In contrast, when focused on “equivocal melanomas,” dermatoscopy without contact with the patient was associated with improper management in about 30% of cases in one study.15 Although the future of teledermatoscopy appears promising for triaging patients, it is an unlikely complete substitute for face-to-face definitive examination of patients with lesions suspicious for malignancy.

While no studies have specifically evaluated the cost-effectiveness of MTD, several studies have indicated store-and-forward systems to be both accurate and cost-effective.16,17 In separate studies, TD services decreased the cost of care in both a rural US community and in Norway.18,19 Due to decreasing equipment costs, much of the existing work on the economic viability of TD services has become obsolete and must be updated. Additionally, potential complicating factors in economic analyses such as these include factors that are difficult to quantify such as the opportunity cost of a patient’s time vs the intangible benefit of an earlier correct diagnosis and wider geographic reach.

**CROSSING BOUNDARIES:**

**TO INCREASE CARE AND MEDICAL EDUCATION RESOURCES IN DEVELOPING COUNTRIES**

Many studies have suggested the potential for TD to increase access to care in developing countries with few dermatologists.20,21 More than 3 billion people live in areas with no access to basic skin treatment. In these regions, 90% of skin diseases are diagnosed and treated by health workers with no formal dermatologic training. The socioeconomic and health implications of TD are significant.22 Some valuable efforts have been made to demonstrate the feasibility of TD and MTD in various parts of Africa.23-26 The sustainable expansion of efforts such as this are encouraged by the fact that patients found this form of dermatology acceptable.27 This expansion, however, will rely on governmental or private agencies to supply equipment, educate participants, and establish relationships between local health care workers and remote dermatologists willing to volunteer in many cases. Efforts to educate additional dermatologists within these regions are also critical at this time.28-30 In addition, efforts must be made in both developed and developing countries to overcome the deficiency of dark skin representation in current medical education resources.31 Together, these efforts would improve the dermatologic care of people with darker skin.

Fortunately, mobile phones with the necessary features for MTD are becoming increasingly affordable. These portable devices are also particularly suitable for developing countries because they have the ability to send data and images from areas where Internet connection is not readily available or is too costly. With store-and-forward capabilities, smart phones make the problem of weak and intermittent network coverage less problematic.
TODAY AND TOMORROW: NOTABLE DEVELOPMENTS AND THE FUTURE OF TD

The advantages of specialized software for the purpose of remote MTD are multifold. First, it provides health care workers an easy-to-follow model to assist them through the TD process. Second, it could include applications that automatically standardize, organize, and share information and images. Interface with electronic medical records will be important as these come online universally. Finally, additional resources can be included to encourage education and the sharing of knowledge with the primary care doctors who send the consults. In Botswana, a pilot program is using SMS texting to search the National Library of Medicine to return disease information to clinicians by phone. Additionally, one member of our group (NC) has recently pioneered the use of diagnostic decision support software (VisualDx, Logical Images, Inc, Rochester, NY), in conjunction with TD and MTD (Figure 2A–C and Figure 3). This integrated combination provides a trusted source of basic skin disease information (including standard diagnostic techniques, management options, and a wide range of comparable images in various skin tones). Importantly, this mobile resource combination also results in empowerment of the primary care doctor both before and after formal consultation with the expert. In a separate pilot project organized through the University of Pennsylvania and sponsored by the American Academy of Dermatology (AAD), MTD projects are underway that use specialized Android phones (Figure 2D). These phones were supplied with both MTD software (ClickDerm, ClickDiagnostics, Inc, Lexington, MA) and visual diagnostic decision support software (VisualDx, Logical Images, Inc, [Figure 2 A–C]) and are being distributed

Figure 2. Example of VisualDx diagnostic decision support-based differential diagnosis page-view on iPad (A). Example of VisualDx disease information page for pemphigus vulgaris (B). Examples of using VisualDx on the IPhone (C). Example of the Nexus One phone use in the American Academy of Dermatology pilot teledermatology program for safety net clinics (D).
to free clinics in underserved areas of the United States. Volunteer dermatologists who are members of the AAD are providing free consultations using the ClickDerm software. An example of the Web-based software interface is shown in Figure 3.

Additional programs using variations of mobile telemedicine are currently underway in various stages. ClickDoc software on the Samsung Soul U900 phone with 5-megapixel cameras is being used effectively for mobile telegenecology in Botswana as a cervical cancer screening study.14 The similar ClickDerm platform is being used in Egypt and Ghana for MTD with good diagnostic concordance.15,16 As robust MTD and diagnostic decision support systems are developed and come online, additional challenges will be discovered. Despite these challenges, multiple groups will continue working on TD applications. Several groups have been established, including The Community for Teledermatology (www.telederm.com), the Africa Teledermatology Project (www.africa.telederm.org), the International Society of Dermoscopy (www.dermoscopy.telederm.org), and Leprosy & Global Dermatology (leprosy.telederm.org). These groups provide free membership and moderated platforms for teleconsultation discussions and services. Currently, these groups are still small and would benefit from greater participation and collaboration. A thriving and open network will enhance development of useful products and services by reducing inefficient redundancies and encouraging collaborations. Similar to the AAD initiative, these groups can also connect dermatologists who are willing to volunteer their consultation to health care workers in remote areas lacking specialists.

CONCLUSIONS

The future of MTD remains promising. With continual technological advancements of MTD devices, the quality and accuracy of care delivered by this modality has constantly increased. Indeed, with improvements of computer-vision science, it will not be long before mobile devices are assisting in diagnosis directly. TD has already been demonstrated to be an effective tool for triage, patient self-management, and remote consultation. As the TD community grows, the practice of MTD will likely be more readily available as a cost-effective means to deliver specialty services and public health interventions to remote regions around the world.

Disclosures: Drs Craft and Ochoa are editors for Logical Images, the makers of VisualDx software.

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Diabetes mellitus (DM) is a well-documented “iceberg” disease. Its worldwide prevalence in adults is 4%, which is likely to rise to 5.4% by 2025. In India, however, the prevalence of DM is 2.4% in rural and 4% to 11.6% in urban dwellers. DM is a heterogeneous group of disorders of carbohydrate and lipid metabolism. There are 3 major types of DM: (1) type I, insulin-dependent diabetes mellitus (IDDM), or juvenile-onset DM, characterized by abrupt onset of symptoms, insulinopenia, dependence on insulin injections, proneness to ketoacidosis, and lack of ability to produce C peptide; (2) type II, noninsulin-dependent diabetes mellitus (NIDDM), or adult-onset diabetes, is recognized by lack of ketoacidosis except under stressful circumstances, ability to produce C peptide, tendency to obesity, and improvement following loss of weight; and (3) type III, secondary diabetes, which occurs as a complication of pancreatic, hormonal, or genetic disorder(s) and/or following ingestion of certain drugs or chemical compounds.

A total of 90% of diabetics have type II diabetes (NIDDM), whereas only 10% have type I diabetes (IDDM). Diabetes is important to study by practicing physicians, including dermatologists, because of the numerous, variedly associated skin manifestations. According to previous estimates, at least 30% to 70% of persons with diabetes have some type of cutaneous involvement during the course of this chronic disease. The prevalence of skin manifestations in diabetics reaches almost 100%, especially when metabolic effects on microcirculation and changes in skin collagen are considered. Although the overall prevalence of cutaneous disorders does not seem to differ between type I and type II diabetes, type II patients develop more frequent cutaneous infections, whereas type I patients frequently develop autoimmune-type cutaneous lesions. Some skin findings can be the presenting manifestation of the disease, while other findings may indicate a serious, even life-threatening issue; furthermore, there are also relatively minor skin manifestations that can potentiate major complications. Recognition of the preceding manifestations is a key to treatment and prevention. Dermatologic disorders associated with DM generally appear after the disease has developed, but they may signal or appear concomitantly with its onset or even precede diabetes by many years. We shall describe the details of diabetes-related dermatoses in parts II and III of this paper to cover the subject in its entirety.

CLASSIFICATION
Understanding DM and its various cutaneous and systemic effects entails knowledge on the part of the treating physician, which starts with prompt and early diagnosis, adequate treatment, and control of diabetes throughout the patient’s life. This management will prevent or ameliorate complications in the
future. Classifying the various dermatoses associated with DM assists in assessing the impact of the disease on body organs and systems at micro and macro levels, providing insight to the treating physician for individualizing treatment for both conditions. Cutaneous markers can also act as a warning that such management has been ignored, thus warranting an immediate reassessment of the patient both clinically and therapeutically to bring the condition under control. Accordingly, it is worthwhile to consider related and/or associated dermatoses in order to manage DM (Table I and Table II).6,12–14

**CLINICAL CONNOTATION OF RELATED DERMATOSES**

**Necrobiosis Lipoidica**

**Historical**

Necrobiosis lipoidica (NL) was first described by M. Oppenheim in 1930, and was subsequently named Necrobiosis lipoidica diabeticorum (NLD) by E. Urbach in 1932.5 Hyperlipidemia seems to play a major role in DM. Goldsmith is quoted to have reported the first case of NL in a nondiabetic patient15; however, it is now well-known that NL is not limited to diabetics.16

**Epidemiology**

NL appears in only 0.3% to 1.6% of patients with diabetes.2 Only 11% to 65% of patients with NL may have DM at the time of diagnosis.16 Of patients without diabetes, 90% eventually develop diabetes and have abnormal glucose tolerance. The female to male ratio is 3:1. The age of onset ranges from birth to 76 years, with an average of 30 years in diabetics and 41 years in nondiabetics. Patients with IDDM develop NL considerably earlier, at a mean age of 22 years, whereas NIDDM and nondiabetic patients develop NL at a mean age of 49 years.12 It is most commonly seen in patients with type I diabetes, but may also occur in patients with type II diabetes.17

**Clinical Appearance**

Typical lesions associated with NL occur on pretibial skin as firm, dull, red, papules or plaques, which may enlarge to form irregular, ovoid plaques with a violaceous, indurated periphery and a yellow atrophic center (Figure 1).15 Lesions on the hands, forearms, abdomen, face, and scalp may also be associated with diabetes.18 Spontaneous remission occurs in 13% to 19% of patients. NL-associated lesions are usually asymptomatic but may involve anesthesia, pain, pruritus, and hypohidrosis of the affected skin.19,20 Ulceration21,22 and squamous cell carcinoma have rarely been reported in areas of NL.23,24

**Pathophysiology**

NL may be associated with microangiopathic changes consisting of thickened basement membranes and capillary walls, particularly in lesions located in the pretibial region. Other proposed causative factors include endarteritis obliterans, immune-mediated vasculitis, delayed hypersensitivity, nonenzymatic glycosylation and other defects in collagen trauma, platelet aggregation, defective mobility of neutrophils, and vascular insufficiency.12,25 A human leukocytic antigen (HLA) correlation has also been found in the form of high frequencies of HLA-DR4, HLA-B8, and HLA-CW3, and low frequencies of HLA-DR5 and HLA-DR7.15,26

**Histopathology**

Two patterns are seen in NL. The first, usually presenting in patients with DM, is called palisading granulomatous, while the second, called tuberculoid, is predominant in the nondiabetic
group. Large areas of necrobiotic collagen are present in the lower two thirds of the dermis, surrounded by a cellular infiltrate of histiocytes, fibroblasts, and lymphoid cells. Extracellular lipid deposits are also seen. Plasma cells are scattered between degenerating fibers with variable numbers of Langhans’ foreign body giant cells, and blood vessels show endothelial proliferation with wall thickening. Atypical lesions have been reported on the face and scalp. Miescher’s granuloma of the face has been suggested for lesions similar to NL but with absence of necrobiosis histopathologically. This has been included in the spectrum of necrobiotic disease. NL has also been seen in association with Crohn’s disease, ulcerative colitis, and following jejunal bypass surgery. An interesting association between NL and GA has been noted and has also been reported to occur with ataxia telangiectasia and sarcoidosis.

Early NL and GA are difficult to differentiate. Late-stage GA lacks the epidermal change, atrophy, or yellow color of NL. GA is typically located on the dorsa of the hands, fingers, and feet. Pigmented pretibial patches associated with diabetes may present as flat, atrophic, hyperpigmented lesions, in contrast to the red or yellow lesions associated with NL. Sarcoi Ordosis may also mimic NL as annular or serpiginous groups of red-brown papules on the scalp, face, or extremities. Rheumatoid nodules can have a clinical appearance similar to NL. Red/yellow indurated plaques and nodules with atrophy and ulceration that involve the periorbital areas characterize necrobiotic xanthogranuloma. It is consistently associated with paraproteinemia.

Treatment

Topical glucocorticoids for early lesions and intralesional injection of glucocorticoids for established lesions are considered first-line therapy. Other treatment modalities include pentoxifylline, chloroquine, and cyclosporine.

GRANULOMA ANNULARE

Historical

GM was first described by T. Colcott Fox in 1895, and was established as a specific entity by H. Radcliffe Crocker. Several studies support the view that generalized GA, especially in older patients, is associated with diabetes. Reports of association of DM with localized variants or localized nodular GA showed that the majority of patients had IDDM. Another study suggested that type II DM and GA have no other association.

Pathophysiology

GA represents a reaction pattern to various triggering factors such as insect bites, waxing-induced pseudofolliculitis, tuberculin

Table II: Classification of Directly/Indirectly Associated Dermatoses

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous manifestations of vascular abnormalities: microangiopathy, macroangiopathy; gangrene; erysipelas-ly erythema</td>
<td>Microangiopathy, macroangiopathy; gangrene; erysipelas-ly erythema</td>
</tr>
<tr>
<td>Cutaneous manifestations of neurologic abnormalities: motor neuropathy, sensory neuropathy; autonomic neuropathy, diabetic foot; eye-foot syndrome</td>
<td>Motor neuropathy, sensory neuropathy; autonomic neuropathy, diabetic foot; eye-foot syndrome</td>
</tr>
<tr>
<td>Cutaneous infections: candidiasis, nonclostridial gas gangrene; dermatophytosis, malignant external otitis; zygomycosis; erythema</td>
<td>Candidiasis, nonclostridial gas gangrene; dermatophytosis, malignant external otitis; zygomycosis; erythema</td>
</tr>
<tr>
<td>Other distinct findings: necrobiosis lipoidica diabeticorum, disseminated granuloma annulare; diabetic neuropathy, diabetic bullae; waxy skin, stiff joints, yellow skin; scleredema of diabetes mellitus, eruptive xanthoma of diabetes</td>
<td>Necrobiosis lipoidica diabeticorum, disseminated granuloma annulare; diabetic neuropathy, diabetic bullae; waxy skin, stiff joints, yellow skin; scleredema of diabetes mellitus, eruptive xanthoma of diabetes</td>
</tr>
<tr>
<td>Less distinct skin findings: skin tags, yellow nails; red face; pigmented purpuric dermatoses; oral findings; peripheral edema</td>
<td>Skin tags, yellow nails; red face; pigmented purpuric dermatoses; oral findings; peripheral edema</td>
</tr>
<tr>
<td>Cutaneous findings in secondary diabetes: hemochromatosis, the lipodystrophies; the cutaneous porphyrias, acanthosis nigricans</td>
<td>Hemochromatosis, the lipodystrophies; the cutaneous porphyrias, acanthosis nigricans</td>
</tr>
<tr>
<td>Dermatoses associated with an increased incidence of diabetes mellitus: Werner’s syndrome, scleroderma; Kaposi’s sarcoma, cutaneous perforating disease; lipid proteinosis, vitiligo; lichen planus</td>
<td>Werner’s syndrome, scleroderma; Kaposi’s sarcoma, cutaneous perforating disease; lipid proteinosis, vitiligo; lichen planus</td>
</tr>
<tr>
<td>Other possible associations with diabetes: alopecia, Dupuytren’s contracture, psoriasis; Degos’ disease, pseudoxanthoma elasticum pruritus; pustulosis palmaris et plantaris; intracutaneous herniation of fat</td>
<td>Alopecia, Dupuytren’s contracture, psoriasis; Degos’ disease, pseudoxanthoma elasticum pruritus; pustulosis palmaris et plantaris; intracutaneous herniation of fat</td>
</tr>
<tr>
<td>Cutaneous reactions to antidiabetic drugs: oral hypoglycemic agents, insulin</td>
<td>Oral hypoglycemic agents, insulin</td>
</tr>
</tbody>
</table>

Figure 1. Necrobiosis lipoidica on the right leg.
test, Bacille Calmette-Guérin vaccination, or hepatitis B vaccination. Infections such as the human papilloma virus, varicella/zoster virus, Epstein-Barr virus, hepatitis C virus, and human immunodeficiency virus have been associated with GA.\textsuperscript{4,40–43} A hypersensitivity mechanism has been implicated due to elevated levels of migration inhibition factor. Lymphocytes, when trapped in the dermis between collagen bundles, may release toxic lysosomal enzymes that cause collagen and elastin degeneration.\textsuperscript{44} A tissue inactivator of neutrophil chemotaxis has also been demonstrated.\textsuperscript{45} Correlation between IDDM and GA has been demonstrated through an HLA-B8 association.\textsuperscript{46}

Epidemiology and Clinical Appearance

GA presents as one or more localized annular or arciform lesions with flesh-colored papular borders and flat centers (Figure 2), most often on the dorsal and lateral aspects of the hand and feet of children and young adults.\textsuperscript{15} Other variants include localized, generalized, perforating, and subcutaneous.\textsuperscript{57} The majority of affected individuals are younger than 30 years; however, the mean age at onset is 51.7 years.\textsuperscript{48} It is twice as common in women as in men.\textsuperscript{5}

Histopathology

Necrobiosis granuloma is seen in three patterns: (1) necrobiotic palisading, (2) interstitial, and (3) sarcoidal or tuberculoid.\textsuperscript{49} There are foci of degenerated collagen in the upper dermis and histiocytes between collagen bundles and around degenerated collagen. The colloidal-iron stain shows abundant mucin in involved areas.\textsuperscript{6} The vessel changes are not predominant, and there are fewer giant cells.\textsuperscript{50} There is a marked reduction or absence of elastic fibers.\textsuperscript{3} Epidermal changes in perforating GA, in the form of superficial areas of necrobiosis surrounded by palisading histiocytes seen below a perforation in the epidermis, have been documented.\textsuperscript{27,31,52}

**CONCLUSIONS**

NIDDM is a widely-acclaimed entity across the globe with far reaching ramifications. The prevalence of skin manifestations in diabetics reaches almost 100%, especially when metabolic effects on microcirculation and changes in skin collagen are considered. NLD and GA are frequently encountered cutaneous expressions. They may either precede or occur during the course of diabetes. It is imperative to take cognizance of these entities, as they may be a forerunner of diabetes and serve as markers of its subsequent management.

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244 Type II Diabetes Mellitus–Related Dermatoses
SELF-TEST REVIEW QUESTIONS

W. Clark Lambert, MD, PhD, Section Editor

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

1) Cutaneous complications of noninsulin-dependent, type 2 diabetes mellitus include: (Answer as many as apply.)
   a. acanthosis nigricans.
   b. acquired perforating dermatosis.
   c. bulla.
   d. carotenoderma.
   e. Dupuytren's contractures.
   f. eruptive xanthomas.
   g. rubeosis facei.

2) Each of the following statements regarding diabetic dermopathy is correct, except: (Choose the single best response.)
   a. bullous lesions are seen very early in most cases.
   b. it is also known as "pigmented pretibial purpura."
   c. it is also known as "shin spots."
   d. it is also known as "spotted leg syndrome."
   e. it characteristically precedes evidence of abnormal glucose metabolism.

3) Which of the following locations is least likely to show yellow dyspigmentation in Carotenoderma? (Choose the single best response.)
   a. Axillae
   b. Brow
   c. Nasolabial folds
   d. Nostrils
   e. Palms and soles
   f. Sclerae
   g. Sebaceous areas.

4) Which of the following entities is more common in women? (Choose the single best response.)
   a. Acquired perforating dermatosis
   b. Bullosis diabeticorum (diabetic bullae)
   c. Diabetic dermopathy
   d. All of the above
   e. None of the above

5) In Rubeosis facei, one may observe: (Answer as many as apply.)
   a. calor (warmth).
   b. elevated borders.
   c. reddening of the face.
   d. reddening of the hands and feet.
   e. telangiectasias.

ANSWERS TO SELF-TEST REVIEW QUESTIONS:

1) a, b, c, d, e, f, g
2) a
3) f
4) e
5) c, d

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Address for Correspondence: W. Clark Lambert, MD, PhD, Room C520 MSB, UMDNJ-NJMS, 185 South Orange Avenue, Newark, NJ 07101 • E-mail: lamberwc@umdnj.edu
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References:

*In vitro activity does not necessarily correlate to in vivo activity.

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The Food and Drug Administration (FDA) has proposed a final sunscreen monograph that is intended to address photostability of sunscreen products. SPF, formerly known as "skin protection factor," will become "sunburn protection factor." SPF label claim will be capped at 50+. The FDA has addressed UV-A exposure and package labeling by proposing two methods of UV-A testing. One method is in vitro and the other is in vivo. On June 17, 2011 the FDA issued a revised notice in the Federal Register rules and regulations advising that the package label claim will not require the four star rating system. The revision will now contain a "broad spectrum" label claim. This will indicate to the consumer that the sunscreen provides UV-B and UV-A protection. To establish a broad spectrum claim the sunscreen will have to pass a critical wavelength test. The threshold for critical wavelength is set at 370 nm. The FDA has concluded that most of the harmful effects from the sun are caused by UV radiation in the range of 290–370 nm. This testing will be referred to as the "broad spectrum test." The prior FDA proposal required a package UV-A label claim requiring a zero to four star rating. A four star rating would have indicated maximum UV-A protection including the UV-A1 spectrum. Achieving a four star rating with a high SPF formulation is extremely challenging using the limited UV-A sunscreens currently permitted by the FDA. Butyl methoxydibenzoylmethane (avobenzone) is the most commonly used organic UV-A sunscreen in the United States. Avobenzone is a photo-unstable agent and must be properly stabilized in sunscreen formulations to provide adequate UV-A protection. The revised FDA requirement acknowledges difficulty achieving protection in the UV-A1 spectrum (340–400 nm) and will no longer propose the four star requirement. The broad spectrum claim with the 370 nm requirement is believed to provide adequate protection based on review of submitted studies.

**WHY IS THERE A NEED FOR SKIN PROTECTION BEYOND SUNSCREENS?**

UV filter molecules absorb and dissipate energy through transfer of energy. When a particle of UV radiation (a photon) transfers its energy, electrons in avobenzone “jump” to a higher energy orbit that is further away from the nuclear framework. The initial jump is frequently to a singlet excited state. The molecule may quickly return to the ground state or go to a triplet excited state. Sunscreen molecules that do not return to the ground state are no longer effective as sunscreen agents. The loss of stability follows a pattern of decline known as an exponential decay curve and is well documented in the literature. Inappropriate formulation of sunscreens, formulating avobenzone with octinoxate, can hasten photoinstability by destroying molecules in both sunscreens. The role of a photostabilizer is to minimize the rate of decay. In addition to rendering a sunscreen formulation ineffective, singlet oxygen is implicated in photosensitization and formation of destructive reactive oxygen species (ROS). This reaction with skin has been associated with textile workers who developed itching, burning sensation, erythema, roughness, dryness, and pigmentation of skin after being in contact with textile dyes that developed singlet oxygen on exposure to light.1–3 Singlet oxygen formation is associated with oxidative damage to amino acids, specifically histidine, tryptophan, and cysteine, as well as nucleic acids, proteins, and lipids.

**ANTIOXIDANTS**

A study was performed4 using two-photon fluorescence imaging of sunscreen formulations containing octocrylene (10%), octylmethoxycinnamate (7.5%), and benzophenone-3 (6.0%) formulated in a simple water-in-oil emulsion. Each sunscreen was tested as a single entity in separate emulsions. Two-photon fluorescence microscopy was used to image UV-induced ROS.
The Next Frontier of Sunscreen Protection

COSMETIC SCIENCE

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**Emblica** (*Emblica officinalis*) has been used for more than 4000 years for a variety of human ailments. *Emblica* has antioxidant activity believed to be related to its high content of low molecular weight tannins. A standardized extract of *Emblica* fruit was evaluated in an SPF 30 sunscreen tested on 39 volunteers who applied the sunscreen formulation at least once per day in place of a moisturizer or sunscreen they would normally use. A positive control group of volunteers used a sunscreen formulation and other moisturizing facial products that they normally used. Evaluation was at baseline and weeks 8 and 12. In addition to the clinical study, an in vitro measurement for matrix metalloproteinase enzyme (MMP)-1, an acute and early biomarker of photoaging, was performed. Test material was Melanoderm skin equivalents (Mat Tek Corporation, Ashland, MA). Melanoderm was exposed to 10 J/cm² UV, a dose equivalent to 2 minimal erythema doses. Enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN) was used to evaluate for MMP-1. Wrinkle and fine-line reduction on the volunteers was documented with evaluation of a trained evaluator who was blinded to location of test and control products. A statistically significant reduction in attenuation of MMP-1 expression was measured in the test material containing sunscreen with the *Emblica* extract.

The study included an SPF 30 broad-spectrum sunscreen without antioxidants. This formulation showed MMP-1 production virtually equivalent to a placebo lotion without sunscreens. Comparable MMP-1 attenuation was also observed with a sunscreen formulation containing diethylhexyl syringylidene malonate. In the in vivo clinical study, the SPF 30 sunscreen lotion containing diethylhexyl syringylidene malonate and the SPF sunscreen formulation containing 0.01% *Emblica* fruit extract both showed visibly reduced wrinkle and fine-line formation compared with the control sunscreens without these ingredients.

**HISTORY OF ANTIOXIDANTS**

In the 1950s, Denham Harman proposed a “free-radical theory” of aging. His hypothesis was that endogenous oxygen radicals were generated in cells, resulting in a pattern of cumulative damage. At the time, this was considered a controversial theory. Approximately 10 years after publication of the free-radical theory, superoxide dismutase, an enzyme with the sole function that seemed to be the removal of superoxide anions, was identified. This discovery provided credence to the Harman theory. The free-radical theory of aging suggested that targets of ROS were random. Current thinking is that ROS act as specific signaling molecules under both physiologic and pathophysiologic conditions. In this regard, ROS are necessary to maintain homeostasis of the body. With regard to photoprotection, the generation of singlet oxygen (\(1^O_2\)) is of particular concern. Singlet oxygen is not considered a free radical as it has no unpaired electron. Rather, it is a highly reactive and potent oxidant as such classified as an ROS. Due to overlapping oxidizing effects, the methods to assess individual ROS lack specificity. The use of several approaches is necessary to obtain insight regarding the relative concentrations and roles antioxidants play in biological systems. Singlet oxygen production is of specific interest to the sunscreen formulator because singlet oxygen in the presence of UV-A radiation has been shown to produce deleterious biological effects. In skin, it will react with urocanic acid resulting in photosensitization and skin aging. The singlet oxygen reaction is short-lived in skin, creating a challenge to measure and establish efficacy claims for the cosmetics industry. It is established that avobenzone, the most commonly used UV-A sunscreen, will form singlet oxygen as a by-product of instability on exposure to UV radiation. Given this possibility, it is important for the formulator to stabilize avobenzone appropriately to minimize this possibility.

Current theory regarding oxidants in the body is that they serve as signal mechanisms important for the organism’s homeostasis. The mechanism of ROS “crosstalk” is not well understood and cannot be easily measured. This is an area currently under scientific investigation.

**CONCLUSIONS**

The proposed final sunscreen monograph establishes standards for testing the effectiveness of sunscreen products and will require labeling that reflects the required test results. Under the...
new regulations a “broad-spectrum” label claim will indicate that the product provides UV-B and UV-A protection. Conceptually the objective is to protect the skin against all types of sun-induced damage. Given that few UV-A sunscreens are available in the United States and it is a challenge to formulate a highly effective sunscreen product that will provide the highest UV-A and UV-B ratings, it is desirable to find additional technologies to help protect skin from solar damage. An example being the need to stabilize avobenzone. The proposed final monograph does not address the potential damaging effects of ROS that are generated in the body as a result of exposure to UV radiation. This is an area of science yet to be fully understood. Our limited ability to measure the biological consequences of excessive ROS production and the resulting paracrine crosstalk are a challenge currently being investigated. Understanding the antioxidant conundrum and developing appropriate antioxidants is indeed the next frontier of photoprotection.

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The Three Faces of Cylindroma

Theresa A. Zaleski, DO;1 Laurie Dabaghian, BA;2 Amin Maghari, MD;3 W. Clark Lambert, MD, PhD3

“What’s in a name? That which we call a rose by any other name would smell as sweet.”


The term cylindroma was first used in 1856 by Billroth to describe an orbital tumor with a glassy appearance.1 The term was derived from the cylindrical appearance of a lesion on cross-section.2 Today, three forms of cylindromas are recognized: a malignant salivary cylindroma also known as adenoid cystic carcinoma, a benign cutaneous cylindroma that occurs in both single and multiple forms, and a malignant cylindroma that usually occurs in the setting of Brooke-Spiegler syndrome.3

While the nomenclature of these lesions may be identical, the clinical behavior and prognosis can vary drastically. It is rare for a benign cutaneous cylindroma to become malignant, but a cylindroma of the salivary glands is almost always malignant.

**CYLINDROMA OF THE SALIVARY GLAND**

Adenoid cystic carcinomas, formerly known as salivary gland cylindromas, are the second most common malignancy in salivary glands, comprising 22% of salivary gland malignancies.4 These tumors are known to have a poor long-term prognosis with a high risk for recurrence.5 The carcinoma may be found in the parotid, submaxillary, and sublingual glands and can develop in any of the minor or major glands of the head, neck, lips, mouth, pharynx, and respiratory tract.6 Histologic findings determine the grade of the tumor. Classically, basaloid cells are found in tubular, solid, or cribriform patterns, and globules of hyaline are interspersed within the cells. Through studying aspirate smears, findings of pleomorphic cells with higher expressions of p53 and Ki-67 and loss of myoepithelial markers suggest a more aggressive and high-grade tumor.7

A tier rank may be used to determine different grades of tumors and help with the differential diagnosis and patient prognosis. Grade I tumors are found in a tubular pattern, grade II tumors are in a cribriform pattern with less than 30% solid areas, and grade III tumors have more than 30% solid basaloid growth (Figure 1).8 The most important histologic feature is the presence and amount of solid areas in the tumor. The carcinomas that contain larger amounts of solid areas and basaloid growth are considered high-grade, and patients have shorter survival rates. Tumors that contain cells in a mixture of tubular and cribriform patterns are more easily excised and have a better prognosis.8 The location of the tumor is also important in the prognosis. Tumors in the palate and parotid gland have a better prognosis, with survival rates at 15 years of 38% and 21%, respectively. Lower survival rates are found in patients with tumors in the submaxillary gland or antrum. The size of the tumor and metastasis may also influence patient prognosis.8 Treatment for this carcinoma is a combination of surgery and radiation therapy. Although radiation therapy has a 96% response rate, it is often not used alone since ACCs have been found to have a 94% local recurrence.5 The survival rate in patients is variable, and metastasis of the tumor has an incidence of 40%.7 Metastasis most commonly takes place in the lungs but can be found in the liver and bone.4 Patients who have metastasis in the lungs have a longer survival rate than those with bone involvement. No major breakthroughs in chemotherapy have been found to treat this tumor.

**BENIGN CUTANEOUS CYLINDROMA OF THE SKIN**

Cutaneous cylindroma is a rare tumor originating from the skin appendages of the scalp and face.9 Benign cylindromas, which are twice as common in women than in men, can occur in both the solitary and multiple form, the latter usually inherited in an autosomal-dominant fashion.10 The observance of multiple cylindromas was first made by Brooke in 1892 and then by Spiegler in 1899.11 Today, the presence of multiple cylindromas is also known as Brooke-Spiegler syndrome, turban tumor, or familial cylindromatosis.12 Brooke-Spiegler syndrome is classified by the appearance of cylindromas, trichoepitheliomas, and occasionally...
The Three Faces of Cylindroma

PERILS OF DERMATOPATHOLOGY

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The Three Faces of Cylindroma

SPIRADENOMAS LOCATED ON THE HEAD AND NECK BEGINNING AS EARLY AS THE SECOND DECADE OF LIFE. The mutation responsible for this syndrome is postulated to be the CLYD gene located on chromosome 16 which displays variable expression but absolute penetrance. On clinical examination, cylindromas appear as slow-growing, firm, pinkish red skin nodules measuring from 2 mm to 6 mm. Histopathologically, benign dermal cylindromas display a jigsaw pattern of epithelial basaloid cell islands with a biphasic cellular distribution surrounded by a thick hyaline-rich stroma, with little or no mitotic figures or nuclear pleomorphism.

The recommended treatment for benign cutaneous cylindromas is surgical excision with wide margins because of the likelihood of local tumor recurrence. Patients, especially those with multiple cylindromas, should be closely followed, however, even after surgical excision to rule out the possibility of recurrence with malignant progression and to undergo early surgical excision before extensive tumor growth. Occasionally, benign cylindromas grow large enough to warrant surgical excision with or without a graft, especially in the case of multiple cylindromas.

MALIGNANT CYLINDROMA OF THE SKIN

Although cutaneous cylindromas are for the most part benign, rarely, cylindromas may become malignant. The first malignant cylindroma was identified by Ancell in 1842. Since that time, only 30 or so cases of malignant cylindroma have been described. When malignant cylindromas do occur, it is usually in the setting of multiple cylindromatosis, a condition seen in Brooke-Spiegler syndrome. Histopathologically, malignant cylindromas differ from their benign counterparts by demonstrating loss of the usual jigsaw pattern seen in benign cylindromas, loss of hyaline sheaths, loss of biphasic cellular distribution, and pronounced cellular pleomorphism with an increased mitotic rate. Clinically, these lesions are heralded by rapid growth, ulceration, and pain, with a propensity for extensive local growth up to 20 cm as well as local recurrence and even the possibility for metastases. Unlike their benign counterpart, malignant cylindromas have the ability to metastasize and may even result in death, thus making early and complete surgical excision with close patient follow-up crucial.

CONCLUSIONS

Although the above three types of cylindromas are categorized under a common name, it is evident that major differences are present that have to be considered when deciding on a treatment plan and prognosis. While it is common thought to associate the term cylindroma with a benign course, this is not always...
true, depending on the type of cylindroma. Even with all three cylindromas having a high likelihood of recurrence, only salivary gland and malignant cutaneous cylindromas have the possibility of metastasis. The initial treatment of the three cylindromas is surgical excision, with close follow-up due to the possibility of recurrence, but in the case of salivary gland carcinomas, radiation is also used as a means of therapy. Prognosis depends on the success of surgical excision, and, in the cases of salivary and malignant cutaneous cylindromas, the extent of metastasis. Above all, the clinician must understand clearly what the pathologist means by a diagnosis of cylindroma.

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Natroba (spinosad) 0.9% topical suspension (ParaPRO LLC, Carmel, IN) was approved by the Food and Drug Administration in January 2011 as a pediculicide indicated for the topical treatment of head lice infestations in patients 4 years and older.1 In the pivotal studies of Natroba, 552 patients were studied and used the medication with a reapplication in 1 week if lice remained; 86% patients were lice free at 14 days, compared with 44% in the placebo control group.2

Spinosad is an antibiotic derived from soil microbes and has long been used for controlling flies that affect animals, killing caterpillars, drywood termites, and preventing infestations of sheep. The spinosyns have a unique mechanism of action involving disruption of nicotinic acetylcholine receptors. When compared with many other insecticides, the spinosyns generally show greater selectivity toward target insects and lesser activity against many beneficial predators as well as mammals and other aquatic and avian animals. Spinosad causes neuronal excitation in insects. After periods of hyperexcitation, lice become paralyzed and die.

Spinosad 0.9% suspension topical suspension (available in 120-mg bottles) is to be used as follows: (1) shake bottle well, (2) apply product to dry scalp and hair using only the amount needed to cover the scalp and hair, (3) rinse off with warm water after 10 minutes, and (4) repeat treatment if live lice are seen 7 days after first treatment. As compared with permethrin 1% (Nix), the current standard treatment for head lice, spinosad requires fewer retreatments. In addition, spinosad does not require nit combing and was significantly more effective than permethrin in 2 studies reflecting actual-use conditions, where most spinosad-treated participants required only 1 application. Spinosad is a more convenient and effective treatment for pediculosis capitis than permethrin.

Natroba is contained in a benzyl alcohol base. Benzyl alcohol also has pediculicidal effects. Benzyl alcohol should not be used in neonates/low-weight children, as it can be systemically absorbed with toxic effect. The most common adverse events (>1%) were application site erythema and ocular erythema.

REFERENCES
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Osteoma cutis represents a disorder characterized by bone formation within the dermis and subcutaneous tissues. Multiple miliary osteoma cutis is a form of osteoma cutis that presents with multiple bony nodules on the face. The disorder can be classified as primary or secondary depending on the absence or presence of associated cutaneous disorders. Primary osteoma cutis is seen mostly in light-skinned, middle-aged to older women without preexisting acne, cutaneous neoplasms, or inflammatory dermatoses. It has also been associated with syndromes such as Albright's hereditary osteodystrophy, Gardner's syndrome, and McCune-Albright syndrome.

In contrast, secondary osteoma cutis is more common and is typically associated with an underlying disorder such as acne vulgaris, basal cell carcinoma, cutaneous inflammation, dermatomyositis, nevi, scleroderma, sebaceous adenoma, trauma, and/or venous stasis. Our patient has primary osteoma cutis of the face. The temporal association of initiating osteoporosis treatment with alendronate and the subsequent development of osteoma cutis raises the possibility that bisphosphonates may be associated with the pathogenesis of this condition in our patient.

While the pathogenesis of osteoma cutis remains unclear, two theories have been proposed to explain the development of the osteomas. One theory suggests that there is a disordered embryologic process that permits mesenchymal cells to differentiate into osteoblasts and migrate to the skin. The second theory speculates that undifferentiated or already mature mesenchymal cells, such as fibroblasts, undergo metaplasia to become osteoblasts.

Treatment of multiple miliary osteoma cutis of the face has been difficult. Topical treatments have been used with varying success. Subjective improvement was described in a 75-year-old African American woman who used 0.1% adapalene gel for 6 months. Also, topical tretinoin therapy for multiple miliary osteoma cutis of the face demonstrated gradual improvement in 3 patients over the course of 3 to 6 months. Our patient did not achieve any significant improvement of her osteoma lesions after applying 12% lactic acid lotion.

Systemic agents have not been successful in the management of this condition. A middle-aged Asian woman with multiple miliary osteomas was treated with oral isotretinoin and did not achieve any improvements. Systemic etidronate disodium treatment was unsuccessful in a 57-year-old woman with osteoma cutis. Similarly, we observed that our patient's lesions appeared after she received bisphosphonate therapy.

There are several reports of successful treatment of miliary osteoma of the face with surgical techniques that remove the bone.
Some investigators meti-epi-ermis to fa-human receptors after the patient began treatment with alendronate for osteoporosis.


Thielen AM, Stucki L, Braun RP, et al. Multiple cutaneous osteomas after beginning systemic therapy with bisphosphonates for osteoporosis. The temporal association between initiation of alendronate and the subsequent development of her facial osteoma cutis raises the possibility that interference with bone absorption may have contributed to pathogenesis of this condition in our patient.

REFERENCES


Figure. Multiple miliary osteoma cutis of the face presenting as numerous, 1- to 2-mm brown, firm papules on the malar cheeks after the patient began treatment with alendronate for osteoporosis.

either from intact skin or following removal of the overlying epidermis. A 46-year-old woman with miliary osteoma cutis unresponsive to topical treatments was treated with a needle microincision-extirpation technique that provided good results that were cosmetically acceptable. Similarly, treatment with incision, curettage, and primary closure showed significant cosmetic improvement with no postinflammatory hyperpigmentation after 10 months in a 64-year-old American Indian/African American woman.

Some investigators have elected to surgically eliminate the epidermis to facilitate osteoma removal. The use of a carbon dioxide continuous wave laser followed by gentle removal of the osteomas with a curette demonstrated resolution of lesions with minimal scarring. Also, dermabration followed by punch biopsy removal of the bony lesions was used in 3 patients with multiple miliary osteoma cutis secondary to acne vulgaris with favorable cosmetic results.
From the Dermato-Venereology (Skin/VD) Centre, Sehgal Nursing Home, Panchwati, Delhi; and the University College of Medical Sciences and Associated GTB Hospital, Delhi, India

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having a chronic relapsing course) may be its eventual clinical expression.\(^3\) Discrepancy of a wide variety of clinical symptoms reported for ACH is a diagnostic dilemma that may require a meticulous workup to exclude several other clinical conditions in its differential diagnosis,\(^4\) including fingertip dermatitis.\(^5\) This seems to be a glaring fallout of recent publications,\(^3,6,7\) and many other articles published in the past, as revealed through a Medlar search\(^8\) of more than 100 published articles. As a result, it is important to evaluate the diagnosis of ACH by performing a Gram stain smear; a bacterial culture of the pustules in vitro, which may either be sterile or grow saprophytic flora that include the *Streptococcus viridans* group, *Enterococcus* species, and diphtheroids\(^6,9\); and KOH examination to exclude the presence of fungus. Similarly, it is necessary to study the microscopic pathology,\(^2\) the details of which were beautifully presented, described, and illustrated by Barber in 1930\(^11\) and subsequently reiterated in 1994.\(^2\)

**CONCLUSIONS**

Excluding other possible etiologies of pustular eruptions involving the fingertips is important before arriving at a diagnosis of ACH. This should ensure an optimal outcome, especially in the setting of current biologics, including tumor necrosis factor \(\beta\) blockers.\(^1,7,8\)

**REFERENCES**


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**Figure 2A.** Section of skin from the tip of the patient's finger showing epithelial hyperplasia, orthokeratosis, and mounds of parakeratosis with a central area of spongiform pustule. Note the fragment of subcutaneous tissue with numerous Pacinian corpuscles (hematoxylin-eosin stain, original magnification ×40).

**Figure 2B.** A higher-power view of the same section showing numerous neutrophils forming microabscesses in the epidermis (hematoxylin-eosin stain, original magnification ×200).
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* Subject to Change
A 53-year-old woman presented with a 20-year history of pruritic dermatitis on the groin, axillae, inframammary folds, posterior aspect of the neck, and popliteal fossae. She was referred to our clinic by an outside facility after results from a punch biopsy diagnosed Hailey-Hailey disease (HHD). The patient had previously attempted treatment with many traditional noninvasive options with no success. Topical treatment modalities included corticosteroids, immunomodulators, antifungals, retinoids, and antibiotic preparations. Intralesional corticosteroids, as well as botulinum toxin and carbon dioxide laser, were also unsuccessful. Failed systemic treatment modalities included antibiotics, antihistamines, prednisone, azathioprine, mycophenolate mofetil, acitretin, isotretinoin, adalimumab, and etanercept. Of note, cyclosporine was successful in clearing the cutaneous involvement in our patient, but elevation of creatinine and exacerbated hypertension precluded continued use. The decision was made to treat the patient by dermabrasion with sandpaper. The patient was prepped in a sterile fashion, and a field block with 1% lidocaine with epinephrine was performed. This was followed by abrasion down to the superficial dermis with 3M Sandblaster fine sandpaper (3M, St. Paul, MN) and hyfrecation between rounds of dermabrasion. The treated areas were then covered with petrolatum and sterile gauze, and antibiotics and pain medication were prescribed. This treatment was initially performed on the patient’s posterior aspect of the neck and later to the bilateral popliteal fossae and axillae. Three months post-treatment, desirable functional and cosmetic results of the treated areas had been achieved (Figure 1 and Figure 2). While no recurrence of clinically active HHD has been seen in the dermabraded areas of the neck and popliteal fossae, the patient continues to have active disease in the axillae despite sandpaper dermabrasion. To quantify our results, we performed two biopsies in the dermabraded sites of the popliteal fossae as healing occurred: a shave biopsy from an obviously active area, and a punch biopsy from a peripheral inactive border. The biopsy from the active area showed diffuse epidermal acantholysis similar to that seen in untreated HHD, while the healing periphery showed only scattered acantholytic areas and a sparse perivascular infiltrate—a marked improvement from the untreated areas.

Hailey-Hailey disease or familial benign chronic pemphigus, is an uncommon autosomal-dominant genodermatosis caused by mutations in the ATP2C1 gene. The disorder is characterized by malodorous, often painful erosions in intertriginous sites. Dysfunction in the protein product hSPCA1 leads to decreased Ca2+ within the Golgi lumen, which may subsequently impair the processing of junctional proteins important in cell-cell adhesion.1 Clinically, patients present with malodorous, macerated patches of acantholytic epidermis, typically in intertriginous areas, that are worsened by heat and diaphoresis.

CONCLUSIONS
The dermatology literature has very little supportive evidence for eradication of HHD by dermabrasion. No reported cases of the efficacy of sandpaper for dermabrasion, which we performed in our patient, were found in a literature review.3 Although successful in only the reported patient, we propose that sandpaper dermabrasion may be a well-tolerated, cost-effective, minimally invasive in-office surgical treatment option for HHD. Further studies and prospective, comparative trials in the future are necessary to confirm or deny this assertion.

Sandpaper dermabrasion seemingly offers long-term disease-free results with minimal recurrences. The main side effects are pain and potential pigmentedary changes and scarring in the treated areas. We experienced more success in treating areas not involving skin folds, making sandpaper dermabrasion more difficult to recommend for areas such as the axillae in HHD.
REFERENCES


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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 glucocorticosteroid 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 include: irritation, folliculitis, acneform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, miliaria and telangiectasia.

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) in this HPA axis study were different from the subject population (mild to moderate atopic dermatitis) and the dosing regimen (two times daily) for which Locoid Lipocream is indicated. Five of the 62 evaluable subjects (8.1%) 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 cosyntropin stimulation. Suppressed subjects ranged in age from 5 months to 16 years and, at the time of enrollment, had 25% to 95% BSA involvement. These subjects did not develop any other signs or symptoms of HPA axis suppression. At the first follow up visit, approximately one month after the conclusion of treatment, cosyntropin stimulation results of all subjects had returned to normal, with the exception of one subject. This last subject recovered adrenal function by the second post treatment visit, 65 days post-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 on the face, underarms, or groin areas unless directed by your physician.

Do not use Locoid Lipocream in the diaper area, as diapers or plastic pants may constitute occlusive dressings.

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Safety and effectiveness in pediatric patients below 3 months of age have not been established. 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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