

# Rochester Criteria Modified for Better Sensitivity

BY ROBERT FINN  
San Francisco Bureau

SAN FRANCISCO — A new, large study has concluded that the Rochester criteria—for determining which febrile infants are at low risk of having a serious bacterial infection—are not as sensitive as once thought.

But with a modification that adds information about the infant's age and viral status, the sensitivity and negative predic-

tive value of the Rochester criteria can be maintained, Dr. Carrie L. Byington said at the annual meeting of the Pediatric Academic Societies.

The prospective cohort study involved 1,779 febrile infants 1-90 days of age. Dr. Byington and her colleagues from the University of Utah, Salt Lake City, analyzed these cases according to the original Rochester criteria, and also evaluated several possible modifications of the criteria.

Developed from data collected in the

1970s and 1980s from 233 infants, the 15 Rochester criteria are based on patient history, physical examination, and laboratory values. Infants with no positive criteria are said to have only a 1.4% risk of serious bacterial infection, while infants with one or more positive criteria are considered to be at high risk, having a 21% chance of serious bacterial infection.

But the Rochester criteria can be unwieldy, and Dr. Byington noted that many physicians routinely make decisions based

on factors that are not part of the criteria, such as the patient's age and viral status.

In the original studies, the Rochester criteria were said to have a sensitivity of 95.7% and a negative predictive value of 99.3%. But in this series of infants seen in Salt Lake City, the Rochester criteria yielded a sensitivity of 90% and a negative predictive value of 97%. By the original criteria, 33% of the infants were said to have a low risk of serious bacterial infection, and 67% were said to have a high risk. As it turned out, only 10% of the infants, whose average age was 31 days, had a serious bacterial infection.

The investigators determined that four of the criteria were significantly associated with serious bacterial illness. They were:

- ▶ A urinalysis with more than 10 white blood cells per high-power field (odds ratio 38.8).
- ▶ An absolute band count greater than 1,500 (odds ratio 2.7).
- ▶ A white blood cell count of less than

*Continued on following page*

## DIFFERIN® (adapalene) Cream, 0.1%

### Rx Only BRIEF SUMMARY

For topical use only. Not for ophthalmic, oral, or intravaginal use.

**INDICATIONS AND USAGE:** DIFFERIN® Cream is indicated for the topical treatment of acne vulgaris.

**CONTRAINDICATIONS:** DIFFERIN® Cream should not be administered to individuals who are hypersensitive to adapalene or any of the components in the cream vehicle.

**PRECAUTIONS: General:** If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose, and mucous membranes. The product should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with adapalene.

**Information for Patients:** Patients using DIFFERIN® Cream should receive the following information and instructions:

1. This medication is to be used only as directed by the physician.
2. It is for external use only.
3. Avoid contact with the eyes, lips, angles of the nose, and mucous membranes.
4. Cleanse area with a mild or soapless cleanser before applying this medication.
5. Moisturizers may be used if necessary; however, products containing alpha hydroxy or glycolic acids should be avoided.
6. Exposure of the eye to this medication may result in reactions such as swelling, conjunctivitis, and eye irritation.
7. This medication should not be applied to cuts, abrasions, eczematous or sunburned skin.
8. Wax epilation should not be performed on treated skin due to the potential for skin erosions.
9. During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of this medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Overall clinical benefit may be noticed after two weeks of therapy, but at least eight weeks are required to obtain consistent beneficial effects.

**Drug Interactions:** As DIFFERIN® Cream has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime rind) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN® Cream. If these preparations have been used, it is advisable not to start therapy with DIFFERIN® Cream until the effects of such preparations in the skin have subsided.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day, and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day. These doses are up to 8 times (mice) and 6 times (rats) in terms of mg/m<sup>2</sup>/day the maximum potential exposure at the recommended topical human dose (MRHD), assumed to be 2.5 grams DIFFERIN® Cream, which is approximately 1.5 mg/m<sup>2</sup> adapalene. In the oral study, increased incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats was observed. No photocarcinogenicity studies were conducted. Animal studies have shown an increased risk of skin neoplasms with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.

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

Reproductive function and fertility studies were conducted in rats administered oral doses of adapalene in amounts up to 20 mg/kg/day (up to 80 times the MRHD based on mg/m<sup>2</sup> comparisons). No effects of adapalene were found on the reproductive performance or fertility of the F<sub>2</sub> males or females. There were also no detectable effects on the growth, development and subsequent reproductive function of the F<sub>1</sub> generation.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN® Cream is administered to a nursing woman.

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

**ADVERSE REACTIONS:** In controlled clinical trials, local cutaneous irritation was monitored in 285 acne patients who used DIFFERIN® Cream once daily for 12 weeks. The frequency and severity of erythema, scaling, dryness, pruritus and burning were assessed during these studies. The incidence of local cutaneous irritation with DIFFERIN® Cream from the controlled clinical studies is provided in the following table:

Incidence of Local Cutaneous Irritation with DIFFERIN® Cream from Controlled Clinical Studies (N=285)				
	None	Mild	Moderate	Severe
Erythema	52% (148)	38% (108)	10% (28)	<1% (1)
Scaling	58% (166)	35% (100)	6% (18)	<1% (1)
Dryness	48% (136)	42% (121)	9% (26)	<1% (2)
Pruritus (persistent)	74% (211)	21% (61)	4% (12)	<1% (1)
Burning/Stinging (persistent)	71% (202)	24% (69)	4% (12)	<1% (2)

Other reported local cutaneous adverse events in patients who used DIFFERIN® Cream once daily included: sunburn (2%), skin discomfort-burning and stinging (1%) and skin irritation (1%). Events occurring in less than 1% of patients treated with DIFFERIN® Cream included: acne flare, dermatitis and contact dermatitis, eyelid edema, conjunctivitis, erythema, pruritus, skin discoloration, rash, and eczema.

**OVERDOSAGE:** DIFFERIN® Cream is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, scaling, or skin discomfort may occur. The acute oral toxicity of DIFFERIN® Cream in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

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325069-0805  
Revised: August 2005

## DIFFERIN® (adapalene gel) Gel, 0.1%

### Rx Only BRIEF SUMMARY

**INDICATIONS AND USAGE:** DIFFERIN® Gel is indicated for the topical treatment of acne vulgaris.

**CONTRAINDICATIONS:** DIFFERIN® Gel should not be administered to individuals who are hypersensitive to adapalene or any of the components in the vehicle gel.

**WARNINGS:** Use of DIFFERIN® Gel should be discontinued if hypersensitivity to any of the ingredients is noted. Patients with sunburn should be advised not to use the product until fully recovered.

**PRECAUTIONS: General:** If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose, and mucous membranes. The product should not be applied to cuts, abrasions, eczematous skin, or sunburned skin.

Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning, or pruritus may be experienced during treatment. These are most likely to occur during the first two to four weeks and will usually lessen with continued use of the medication. Depending upon the severity of adverse events, patients should be instructed to reduce the frequency of application or discontinue use.

**Drug Interactions:** As DIFFERIN® Gel has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN® Gel. If these preparations have been used, it is advisable not to start therapy with DIFFERIN® Gel until the effects of such preparations in the skin have subsided.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.3, 0.9, and 2.6 mg/kg/day and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day, approximately 4-75 times the maximal daily human topical dose. In the oral study, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats, and in the incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats.

No photocarcinogenicity studies were conducted. 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 to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.

In a series of *in vivo* and *in vitro* studies, adapalene did not exhibit mutagenic or genotoxic activities.

**Pregnancy:** Teratogenic effects. Pregnancy Category C. No teratogenic effects were seen in rats at oral doses of adapalene 0.15 to 5.0 mg/kg/day, up to 120 times the maximal daily human topical dose. Cutaneous route teratology studies conducted in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, up to 150 times the maximal daily human topical dose exhibited no fetotoxicity and only minimal increases in supernumerary ribs in rats. There are no adequate and well-controlled studies in pregnant women. Adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN® Gel is administered to a nursing woman.

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

**ADVERSE REACTIONS:** Some adverse effects such as erythema, scaling, dryness, pruritus, and burning will occur in 10-40% of patients. Pruritus or burning immediately after application also occurs in approximately 20% of patients. The following additional adverse experiences were reported in approximately 1% or less of patients: skin irritation, burning/stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of DIFFERIN® Gel during clinical trials were reversible upon discontinuation of therapy.

**OVERDOSAGE:** DIFFERIN® Gel is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, scaling, or discomfort may occur. The acute oral toxicity of DIFFERIN® Gel in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

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325034-0903  
Revised: September 2003

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DIF-656 Printed in USA 01/06

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## Routine Interval Appendectomy Unnecessary?

HILTON HEAD ISLAND, S.C. — Interval appendectomy may be unnecessary after a bout of medically managed appendicitis in children, Dr. Devin Puapong said at the annual meeting of the American Pediatric Surgical Association.

Surgeons often cite a high risk of recurrence as the primary reason for an elective interval appendectomy. But according to Dr. Puapong of the Kaiser Permanente Los Angeles Medical Center, "Recurrence of appendicitis after initial nonoperative treatment is very uncommon and not associated with any major complications. We feel [interval appendectomy] may not be necessary."

Dr. Puapong conducted a retrospective study of Kaiser's medical records database, which included 6,446 children treated for appendicitis from 1992 to 2002.

Of those, only 72 were initially managed with medical therapy; 11 went on to have an interval appendectomy, and the other 61 were observed. The length of stay in the observed patients was significantly longer (15 days vs. 7 days).

Over a mean follow-up of 7.5 years, there were only five recurrences of appendicitis (a rate of 8%). All recurrences occurred within 1 year and most were within 2-3 months, Dr. Puapong said.

Four of the recurrences were in patients who presented with an initial abscess, but because of the small number, the association was not statistically significant. Nor were age, gender, type of initial appendicitis, and drainage of initial abscess significantly associated with recurrence. No major complications were observed in any of the patients with recurrence, although two were found to have a prolonged ileum.

—Michele G. Sullivan