

# Superinfection Itches for Antibiotics, Barrier Repair

BY BETSY BATES

Los Angeles Bureau

DENVER — Any child with atopic dermatitis who has increasing pain, erythema, edema, heat, and purulent exudate is superinfected and requires antibiotics and emollients, according to an expert in pediatric dermatology.

A culture is necessary only for prescribing the correct antibiotic.

"I'm here to plead with you that infec-

tion is a clinical diagnosis, not a microbiological diagnosis," said Dr. H. Alan Arbuckle, a dermatologist and pediatrician at the University of Colorado, Denver, and Children's Hospital in Aurora, Colo.

"Doing a culture in a superinfected AD kid is worthless if your goal is to make the diagnosis of infection.

"All of these kids are going to be colonized. All are going to be positive. If you tell me the age of the wound, I'll tell you what organisms are in there, because if

you look at acute and chronic wounds, they march through a sequential order of which organisms are present," he said. The increasingly relevant purpose of doing a culture on such a child is to direct antibiotic therapy by determining sensitivities of the involved organisms.

"All children with AD are colonized with staph [*Staphylococcus*] and strep [*Streptococcus*], predominantly *Staph aureus* and *Strep pyogenes*," he said at a meeting on pediatric hospital medicine.

Recent research findings provide perspective on the course of severe atopic dermatitis, according to Dr. Arbuckle.

Most pivotally, the evidence is mounting that "the problem in atopic dermatitis is . . . an abnormal barrier function," he said at the meeting, which was sponsored by the Society of Hospital Medicine, the American Academy of Pediatrics, and the American Pediatric Association.

In years past, pediatric dermatologists argued with pediatric allergists over the primary etiology of atopic dermatitis, with allergists arguing that immune dysfunction was to blame.

The issue was put to rest when Japanese researchers discovered that the vast majority of children with atopic dermatitis have a genetic defect in filaggrin, a protein that bundles keratin and provides the "mortar" in the brick-and-mortar type construction of the stratum corneum.

"We kind of had a big kumbaya, kissed, and made up. Dermatologists [had always said], well, there is an immune component, but how did the antigen get there? It got there because [the skin] had an improper barrier," Dr. Arbuckle commented.

Microcracks and microfissures, exacerbated by itching prompted by exposed nerve fibers in the epidermis, open the door to allergens, bacteria, and viruses. Compounding the problem is transepidermal water loss 600 times normal in the skin of children and adults with atopic dermatitis.

"We always knew that atopic kids have higher colony counts even when they aren't superinfected," said Dr. Arbuckle. "[It turns out], *S. aureus* is very adaptable, and upregulates certain adhesion proteins in a very dry environment."

Treatment is imperative in the face of superinfection, because children can harbor a profound bacterial load and develop sepsis, Dr. Arbuckle emphasized.

First-generation cephalosporins are "probably fine" as a first-line choice, but it depends on one's community and culture results, he said.

Once a proper antibiotic is selected, "You've got to restore barrier function. If you don't do this, they're not going to get better," Dr. Arbuckle emphasized.

In Denver's dry climate, he said he prefers petrolatum-based products, the simpler the better to avoid allergic responses. Plain petroleum jelly contains no lanolin or other additives that might cause a reaction. Choose topical steroids in ointment form, because creams often contain propylene glycol, which "stings like Hades," he suggested.

The "biggest failure" of most physicians is undertreatment of pruritus, which is often so severe it can preclude rapid eye movement sleep. Sedating antihistamines should be prescribed for night time and nonsedating antihistamines in the morning.

"Children with atopic dermatitis are perennially, horrifically itchy," he said, noting that he tells residents that if they prescribe an antihistamine as needed, "I will slap you upside the head."

Dr. Arbuckle disclosed no relevant conflicts of interest regarding any product used to treat atopic dermatitis. ■

## ClindaReach™

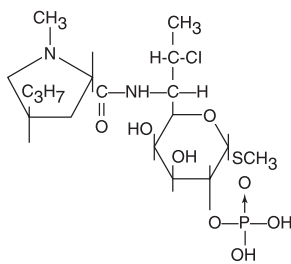
(Clindamycin Phosphate Topical Solution USP, 1%) Pledgets  
For External Use Only

### DESCRIPTION

ClindaReach™ (Clindamycin Phosphate Topical Solution USP, 1%), Pledgets (ClindaReach™) contain clindamycin phosphate, USP at a concentration equivalent to 10 mg clindamycin per milliliter. Each ClindaReach™ pledget applicator contains approximately 1 mL of topical solution.

Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

The solution contains isopropyl alcohol 50% v/v, propylene glycol, sodium hydroxide (to adjust the pH to between 4.0–7.0) and purified water. The structural formula is represented below:



The chemical name for clindamycin phosphate is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2- (dihydrogen phosphate). It has a molecular weight of 504.96, and the molecular formula is C<sub>18</sub>H<sub>34</sub>ClN<sub>2</sub>O<sub>8</sub>PS. Flash point 75°F.

### CLINICAL PHARMACOLOGY

Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

Following multiple topical applications of clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per mL in an isopropyl alcohol and water solution, very low levels of clindamycin are present in the serum (0–3 ng/mL) and less than 0.2% of the dose is recovered in urine as clindamycin.

Clindamycin activity has been demonstrated in comedones from acne patients. The mean concentration of antibiotic activity in extracted comedones after application of Clindamycin Phosphate Topical Solution for 4 weeks was 597 mcg/g of comedonal material (range 0–1490). Clindamycin *in vitro* inhibits all *Propionibacterium acnes* cultures tested (MICs 0.4 mcg/mL). Free fatty acids on the skin surface have been decreased from approximately 14% to 2% following application of clindamycin.

### INDICATIONS AND USAGE

ClindaReach™ is indicated in the treatment of acne vulgaris. In view of the potential for diarrhea, bloody diarrhea and pseudomembranous colitis, the physician should consider whether other agents are more appropriate. (See CONTRAINDICATIONS, WARNINGS and ADVERSE REACTIONS.)

### CONTRAINDICATIONS

ClindaReach™ is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of 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 clostridia 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 *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea.

Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 milligrams to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parenteral therapy with clindamycin.

### PRECAUTIONS

#### General

ClindaReach™ contains an alcohol base that will cause burning and irritation of the eye. In the event of accidental contact with sensitive surfaces (eye, abraded skin, mucous membranes), bathe with copious amounts of cool tap water. The solution has an unpleasant taste and caution should be exercised when applying medication around the mouth.

ClindaReach™ should be prescribed with caution in atopic individuals.

#### Drug Interactions

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore it should be used with caution in patients receiving such agents.

#### Pregnancy: Teratogenic Effects—Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin ranging from 100 to 600 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to clindamycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

#### Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of ClindaReach™. 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 in pediatric patients under the age of 12 have not been established.

### ADVERSE REACTIONS

In 18 clinical studies of various formulations of topical Clindamycin Phosphate using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events [see table below].

Treatment Emergent Adverse Event	Number of Patients Reporting Events		
	Solution n=553 (%)	Gel n=148 (%)	Lotion n=160 (%)
Burning	62 (11)	15 (10)	17 (11)
Itching	36 (7)	15 (10)	17 (11)
Burning/Itching	60 (11)	# (–)	# (–)
Dryness	105 (19)	34 (23)	29 (18)
Erythema	86 (16)	10 (7)	22 (14)
Oiliness/Oily Skin	8 (1)	26 (18)	12* (10)
Peeling	61 (11)	# (–)	11 (7)

# not recorded

\* of 126 subjects

Orally and parenterally administered clindamycin has been associated with severe colitis which may end fatally.

Cases of diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulations of clindamycin and rarely with topical clindamycin (see WARNINGS).

Abdominal pain and gastrointestinal disturbances as well as gram-negative folliculitis have also been reported in association with the use of topical formulations of clindamycin.

### OVERDOSAGE

Topically applied ClindaReach™ can be absorbed in sufficient amounts to produce systemic effects. (See WARNINGS.)

### DOSAGE AND ADMINISTRATION

Apply a thin film of ClindaReach™ twice daily to affected area. More than one pledget may be used. Each pledget should be used only once and then be discarded.

Pledget: Remove pledget from jar just before use. Do not use if the seal under the cap is broken. Discard after single use.

Keep all liquid dosage forms in containers tightly closed.

### HOW SUPPLIED

ClindaReach™ Pledgets contain Clindamycin Phosphate Topical Solution. The solution contains Clindamycin Phosphate equivalent to 10 mg clindamycin per milliliter.

ClindaReach™ is supplied as 120 single use pledgets, packaged as two jars of 60 single use pledgets each.

Store at controlled room temperature 15° to 30°C (59° to 86°F) [See USP]. Protect from freezing. Flash Point 75°F.

### Rx only

Manufactured for: Sirius Laboratories,  
a wholly owned subsidiary of DUSA Pharmaceuticals, Inc., 25 Upton Dr, Wilmington, MA 01887

DUSA®

Manufactured by:  
PERRIGO, Bronx, NY 10457  
Patent pending

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