

Fever in Child Less Than 2 Years Old? Think UTI

BY TIMOTHY F. KIRN
Sacramento Bureau

INCLINE VALLEY, NEV. — Urinary tract infection is so common in children younger than age 2 years that a physician should almost always get a urine culture when working up a fever in a child that age, Dr. Nathan Kuppermann said at an emergency medicine conference sponsored by the University of California, Davis.

That includes getting a urine culture for febrile children younger than age 2 years who have a clinically documented viral infection, he said.

“Urinary tract infections in young febrile infants, particularly, are very common, and these viral infections are very common, so overlap occurs not infrequently,” said Dr. Kuppermann, professor of emergency medicine and pediatrics and chair of the department of emergency medicine at the university.

Studies have looked at concurrence of bacterial infection and viral croup, varicella, stomatitis, bronchiolitis, and influenza infection, and they suggest that a urinary tract infection can also be present about 3% of the time, he said.

Urinary tract infection (UTI) is probably the most important bacterial infection in children 0-3 months of age, because it is so common and because of its serious consequences. Urinary tract infection occurs in 5%-10% of children aged 0-3

months who have a fever above 38° C.

About half the time, the normal routine urinalysis performed for a child of that age will be normal even when there is an infection, Dr. Kuppermann noted. So, one should have a culture done, with Gram staining.

In children younger than age 3 months, UTI is more common in boys than girls. It only switches when they get older. In children younger than age 2 years overall, UTI accounts for 7%-8% of infections in girls with a temperature of 39° C or higher, and 2%-3% of boys with a temperature of 39° C or higher. Most of those boys, however, are uncircumcised. The rate among circumcised boys is 0.2%-0.4%, Dr. Kuppermann said.

The reason for the UTI vigilance is that the kidney is so much more susceptible to damage in the young. It is estimated that most UTIs that lead to renal damage occur in children younger than age 4 years, and especially in those younger than 1 year.

Approximately 13%-15% of end-stage renal disease may be related to an unrecognized, and untreated, UTI in early childhood, Dr. Kuppermann said.

DTaP Vaccine Now Cleared for All Five Doses

The diphtheria, tetanus and acellular pertussis (DTaP) vaccine manufactured by Sanofi-Pasteur was approved last month for use as the fifth consecutive dose of the vaccine series in children aged 4 through 6 years, following four previous doses of the same vaccine.

The vaccine, marketed as DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) by Sanofi-Pasteur, was approved for four consecutive doses in 2002, administered at 2, 4, 6, and 15-20 months of age. The Food and Drug Administration approved the fifth dose last month, based on safety data and booster responses in a study of more than 400 children for the 4- to 6-year-old dose at 22 different sites, according to Sanofi-Pasteur.

From a practical standpoint, this approval allows pediatricians using DAPTACEL to stock one brand of the vaccine in the refrigerator for use for all five doses, Dr. Robert W. FrencK Jr., professor of pediatrics, Cincinnati Children’s Hospital Medical Center, said in an interview.

Although there is no scientific reason to suspect that using different brand vaccines for a vaccine series in a child would be ineffective, “from a purist standpoint, if you can use the same vaccine for the whole series, you may argue that it may have some benefit,” added Dr. FrencK, a member of the American Academy of Pediatrics’ Committee on Infectious Diseases.

He was not involved in DAPTACEL studies and had no conflicts to disclose.

—Elizabeth Mechatie

BenzaClin® Topical Gel

(clindamycin - benzoyl peroxide gel)

Brief summary. Please see full prescribing information for complete product information.
Topical Gel: clindamycin (1%) as clindamycin phosphate, benzoyl peroxide (5%)
For Dermatological Use Only - Not for Ophthalmic Use
Reconstitute Before Dispensing

INDICATIONS AND USAGE
BenzaClin Topical Gel is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS
BenzaClin 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, 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 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. 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 *C. 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 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.

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 vitro* antagonism is not known.

- Information for Patients:** Patients using **BenzaClin Topical Gel** should receive the following information and instructions:
- BenzaClin 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.
 - This medication should not be used for any disorder other than that for which it was prescribed.
 - Patients should not use any other topical acne preparation unless otherwise directed by physician.
 - Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using BenzaClin Topical Gel. To minimize exposure to sunlight, a wide-brimmed hat or other protective clothing should be worn, and a sunscreen with SPF 15 rating or higher should be used.
 - Patients should report any signs of local adverse reactions to their physician.
 - BenzaClin Topical Gel** may bleach hair or colored fabric.
 - BenzaClin Topical Gel** can be stored at room temperature up to 25°C (77°F) for 3 months. Do not freeze. Discard any unused product after 3 months.
 - Before applying **BenzaClin Topical Gel** to affected areas wash the skin gently, then rinse with warm water and pat dry.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced skin tumors in transgenic Tg.AC mice in a study using 20 weeks of topical treatment.

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

In a 2-year dermal carcinogenicity study in rats, treatment with BenzaClin Topical Gel at doses of 100, 500 and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats. The incidence of keratoacanthoma at the treated site of males treated with 2000 mg/kg/day (8 times the highest recommended adult human dose of 2.5 g BenzaClin Topical Gel, based on mg/m²) was statistically significantly higher than that in the sham- and vehicle-controls.

Genotoxicity studies were not conducted with BenzaClin Topical Gel. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Clindamycin phosphate sulfoxide, an oxidative degradation product of clindamycin phosphate and benzoyl peroxide, was not clastogenic in a mouse micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. 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 **BenzaClin 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 BenzaClin Topical Gel, based on mg/m²) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C:
Animal reproductive/developmental toxicity studies have not been conducted with BenzaClin Topical Gel or benzoyl peroxide. Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times 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.

There are no well-controlled trials in pregnant women treated with **BenzaClin Topical Gel**. It also is not known whether **BenzaClin Topical Gel** can cause fetal harm when administered to a pregnant woman.

Nursing Women: It is not known whether **BenzaClin Topical Gel** is excreted in 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, the most frequently reported adverse event in the BenzaClin treatment group was dry skin (12%). The Table below lists local adverse events reported by at least 1% of patients in the BenzaClin and vehicle groups.

Local Adverse Events - all causalities in >= 1% of patients		
	BenzaClin n = 420	Vehicle n = 168
Application site reaction	13 (3%)	1 (<1%)
Dry skin	50 (12%)	10 (6%)
Pruritus	8 (2%)	1 (<1%)
Peeling	9 (2%)	-
Erythema	6 (1%)	1 (<1%)
Sunburn	5 (1%)	-

The actual incidence of dry skin might have been greater were it not for the use of a moisturizer in these studies.

DOSAGE AND ADMINISTRATION
BenzaClin Topical Gel should be applied twice daily, morning and evening, or as directed by a physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry.

Size (Net Weight)	NDC 0066-	Benzoyl Peroxide Gel	Active Clindamycin Powder (In plastic vial)	Purified Water To Be Added to each vial
25 grams	0494-25	19.7g	0.3g	5 mL
50 grams	0494-50	41.4g	0.6 g	10 mL
50 grams (pump)	0494-55	41.4g	0.6 g	10 mL

Prior to dispensing, tap the vial until powder flows freely. Add indicated amount of purified water to the vial (to the mark) and immediately shake to completely dissolve clindamycin. If needed, add additional purified water to bring level up to the mark. Add the solution in the vial to the gel and stir until homogenous in appearance (1 to 1 1/2 minutes). For the 50 gram pump only, reassemble jar with pump dispenser. **BenzaClin Topical Gel** (as reconstituted) can be stored at room temperature up to 25°C (77°F) for 3 months. Place a 3 month expiration date on the label immediately following mixing.

Store at room temperature up to 25°C (77°F) [See USP].
Do not freeze. Keep tightly closed. Keep out of the reach of children.

US Patents 5,446,028; 5,767,098; 6,013,637

Brief Summary of Prescribing Information as of May 2007.
Rx Only

Dermik Laboratories
a business of sanofi-aventis U.S. LLC
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