

CLINICAL CAPSULES

Erythromycin Resistance in *S. pyogenes*

Macrolide prescriptions within 1 year of throat culture were significant predictors of erythromycin-resistant *Streptococcus pyogenes* in a study of 1,225 children, reported Dr. Carlo Gagliotti of the Agenzia Sanitaria Regionale Emilia-Romagna in Bologna, Italy, and his associates.

The study included children aged 0-14 years who had at least one throat swab culture that was positive for *S. pyogenes* during 2003 (CID 2006;42:1153-6).

Overall, the average prevalence of erythromycin resistance was 25%. Among chil-

dren who were given azithromycin within 1 month of culture, 2-3 months of culture, and 4-12 months of culture, the prevalence of erythromycin resistance was 67%, 44%, and 23%, respectively.

Among children who were given macrolides other than azithromycin at the same intervals, the prevalence of erythromycin resistance was 41%, 38%, and 20%, respectively. The long half-life of azithromycin may have contributed to the significant difference between azithromycin and other macrolides, the investigators noted.

By contrast, the resistance rate was only 21% among the 818 children who had not received a macrolide within 1 year of their throat swabs. Overall, the odds ratios of erythromycin resistance during the 3 months prior to throat swab cultures were 5.0 for children who were given azithromycin and 2.2 for children who were given other macrolides, compared with children who did not receive macrolides.

Multiple Vaccines Pose Minimal Risk

The measles, mumps, rubella, and varicella vaccine can be given concomitantly with other childhood vaccines, reported Dr.

Henry Shinefield of the University of California, San Francisco, and his colleagues.

The researchers conducted an open, multicenter trial in which 1,779 healthy children aged 11-16 months were randomized into three groups. Group 1 received the measles, mumps, rubella, and varicella vaccine (MMRV), the combined *Haemophilus influenzae* type b conjugate-hepatitis B vaccine (HH), and the combined diphtheria-tetanus-acellular pertussis vaccine (DTaP) at the same visit. Group 2 received the MMRV at the initial visit, followed by HH and DTaP 42 days later. Group 3 received separate MMR and varicella vaccines at the initial visit, followed by HH and DTaP 42 days later.

Overall, the antibody response rates and geometric mean antibody titers to measles, mumps, rubella, and varicella were similar whether MMRV was given at the same time as the other vaccines or 42 days earlier. When MMRV was given at the same time as HH and DTaP, the antibody response rates for measles, mumps, rubella, and varicella were 97.8%, 95.4%, 98.6%, and 89.7%—higher than the previously established acceptability criteria.

Children who received all the vaccines at once were significantly more likely to report pain or tenderness at the injection site, compared with the other groups.

Dr. Shinefield has received an honorarium for preparing informational material about the MMRV vaccine ProQuad, and is a member of the Merck Advisory Committee on Varicella and ProQuad.

Molecular Diagnosis in Empyema

Molecular diagnosis improved detection of bacteria in 28% of children with pleural empyema and in 43% of those with empyema resulting from *Streptococcus pneumoniae*, reported Dr. Alban Le Monnier of the Assistance Publique-Hôpital de Paris, France, and his colleagues.

The molecular diagnostic techniques of broad-range 16S ribosomal DNA (rDNA) polymerase chain reaction (PCR) and pneumococcal antigen detection have been validated for urine and cerebrospinal fluid samples, but had not been validated for pleural fluid (CID 2006;42:1135-40).

Pleural fluid specimens were collected from 78 children with pleural empyema aged 15 years and younger (median age 3.9 years) in a prospective 4-year study from January 2001 to December 2004.

Overall, 60 of the 78 cases of empyema (77%) were microbiologically confirmed either by culture or by 16S rDNA PCR, and 40 (51%) were found to have pneumococcal origins. Conventional microbiologic culture identified pneumococcal strains in 23 of these 40 cases (58%). A total of 20 of these 23 cases also tested positive for *S. pneumoniae* using the 16S rDNA PCR and pneumolysin PCR techniques.

The diagnosis of *S. pneumoniae* was obtained by 16S rDNA PCR alone in 17 of the 40 cases (43%), all of whom had received antibiotics prior to pleural fluid aspiration.

No bacterial association with empyema could be found either by culture or PCR in 18 patients (23%), 16 of whom had received antibiotics prior to testing. Although the molecular tests are not a substitute for standard cultures, they can provide rapid results that allow clinicians to quickly adapt antibiotic therapy, they said.

—Heidi Splette

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Duac® Topical Gel

(clindamycin, 1% - benzoyl peroxide, 5%)

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 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 *Clostridium 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 *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 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 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.
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, rinse 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. The clinical significance of this is unknown.

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

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:

	Local reactions with use of Duac Topical Gel % of patients using Duac Topical Gel with symptom present Combined results from 5 studies (n = 397)					
	Before Treatment (Baseline)			During Treatment		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	28%	3%	0	26%	5%	0
Peeling	6%	<1%	0	17%	2%	0
Burning	3%	<1%	0	5%	<1%	0
Dryness	6%	<1%	0	15%	1%	0

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

HOW SUPPLIED

Duac® (clindamycin, 1% - benzoyl peroxide, 5%) Topical Gel is available in a 45 gram tube - NDC 0145-2371-05.

Prior to Dispensing: Store in a cold place, preferably in a refrigerator, between 2°C and 8°C (36°F and 46°F). Do not freeze.

Dispensing Instructions for the Pharmacist: Dispense Duac Topical Gel with a 60 day expiration date and specify "Store at room temperature up to 25°C (77°F). Do not freeze."

Keep tube tightly closed. Keep out of the reach of small children.

U.S. Patent Nos. 5,466,446, 5,446,028, 5,767,098, and 6,013,637
Patent Pending



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833185 Rev. 0504

REFERENCES: 1. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. *Am Acad Derm.* 1997;37:590-595. 2. Tangheiti EA, Gold MH. A Two-center patient preference study comparing two benzoyl peroxide/clindamycin gels in acne vulgaris patients. Poster presented at: 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA. Poster 108. 3. Tangheiti EA, Abramovits W, Solomon B, et al. Tazarotene versus tazarotene plus clindamycin/benzoyl peroxide in the treatment of acne vulgaris: a multicenter, double-blind, randomized parallel group trial. Poster presented at: 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA. Poster 147.

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