

# International Adoptees May Bring Medical Issues

BY LAIRD HARRISON

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

SAN FRANCISCO – It's hard to grow up in an orphanage – literally. Small stature figures prominently on a growing list of problems that children adopted from abroad bring to the United States, according to two adoption specialists.

“More children are being placed in-country,” said Dr. Elaine Schulte, medical director of the International Adoption Program at the Cleveland Clinic Children's Hospital, one of two speakers who outlined current trends in international adoption at the meeting. “Fewer healthy children are available for international adoption, and families are pushed to accept sicker children.”

The number of foreign adoptions to

the United States has dropped roughly in half from 2004 to 2009, when it reached 12,753, according to figures from the U.S. Department of State that were cited by Dr. Schulte.

Those children available are more likely to come with serious medical problems. Among the most common are cleft lip and palate, congenital heart disease, Down syndrome, orthopedic problems, amniotic band deformities, and infectious

disease such as hepatitis B and C and HIV.

Only 20% of internationally adopted children have no special medical or developmental issues; in 60%, these problems are mild to moderate and in the rest, severe, Dr. Schulte said.

Even before birth, most of these children suffer from their mother's substance exposures, malnutrition, or stress. After birth, some live through periods of abandonment before being taken into an orphanage.

When they arrive, they often face further malnutrition, abuse, and neglect because even well-intentioned caregivers don't have all the resources the children need, Dr. Schulte said. “These kids don't get talked to,” she said, displaying a photograph of children confined in rows of metal cribs in a barren room. “They lie in bed staring at the ceiling.”

Children coming from foster care generally fare better, but they may have changed homes frequently, leaving them with fear of abandonment.

Families who want to adopt get very little information about the children's backgrounds and health, and are getting even less time than in the past to decide whether to take these children home.

The adoption process itself can lead to health issues. The adopting families may encounter infectious diseases in the general population of the child's country, and they may be infected by the child they are adopting. “I always remind them that they have to take care of themselves,” said Dr. Schulte, herself the mother of two children adopted from China. “What are you going to do if you get sick, and you have to take care of the child?”

For example, 106 out of 100,000 children adopted from abroad carry hepatitis A, compared with 1 in 100,000 in the general population, she said. So the Centers for Disease Control and Prevention now recommends vaccination for this disease for anyone who will have close contact with a child arriving from a country with endemic hepatitis A. Dr. Schulte recommended hepatitis B immunization as well.

With such precautions in mind, the pediatrician should begin counseling the family before the adoption. A physician can help the family interpret whatever health records are available and formulate more questions. Dr. Schulte gave the example of a child whose photograph suggested fetal alcohol syndrome.

The physician also can prepare the family with community resources, such as a referral to an adoption specialist. (The American Academy of Pediatrics has a directory of such specialists.)

Physicians should schedule their first visits with adopted children a week or two after the children arrive home. If it's sooner than that, the parents will be too exhausted and won't have had time to closely observe their new children.

Dr. Schulte advised allowing at least 30 minutes for the appointment, because it's so important to carefully examine the child and query the new parents. The vis-

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## BRIEF SUMMARY

### VELTIN™ (clindamycin phosphate and tretinoin) Gel 1.2%/0.025%

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

#### 1 INDICATIONS AND USAGE

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

#### 4 CONTRAINDICATIONS

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

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 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 opiates 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.

##### 5.2 Ultraviolet Light and Environmental Exposure

Exposure to sunlight, including sunlamps, should be avoided during the use of VELTIN Gel, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight 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 particular caution. 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.

#### 6 ADVERSE REACTIONS

##### 6.1 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 ( $\geq 1\%$ ) 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 of treatment in patients exposed to VELTIN Gel. At baseline (N=476), local skin reactions included erythema (24%), scaling (8%), dryness (11%), burning (8%), and itching (17%). At 12 weeks of treatment (N=409), local skin reactions included erythema (21%), scaling (19%), dryness (22%), burning (13%), and itching (15%). During the 12 weeks of treatment, each local skin reaction peaked at week 2 and gradually reduced thereafter.

#### 7 DRUG INTERACTIONS

##### 7.1 Erythromycin

VELTIN Gel should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component. *In vitro* studies have shown antagonism between these 2 antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

##### 7.2 Neuromuscular Blocking Agents

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

#### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

Pregnancy Category C. There are no well-controlled studies in pregnant women treated with VELTIN Gel. VELTIN Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A limit teratology study performed in Sprague Dawley rats treated topically with VELTIN Gel or 0.025% tretinoin gel at a dose of 2 mL/kg during gestation days 6 to 15 did not result in teratogenic effects. Although no systemic levels of tretinoin were detected, craniofacial and heart abnormalities were described in drug-treated groups. These abnormalities are consistent with retinoid effects and occurred at 16 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison. For purposes of comparison of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of VELTIN Gel applied daily to a 50 kg person.

*Tretinoin:* Oral tretinoin has been shown to be teratogenic in mice, rats, hamsters, rabbits, and primates. It was teratogenic and fetotoxic in Wistar rats when given orally at doses greater than 1 mg/kg/day (32 times the recommended clinical dose based on body surface area comparison). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgous monkey, a species in which tretinoin metabolism is closer to humans than in other species examined, fetal malformations were reported at oral doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (324 times the recommended clinical dose based on body surface area comparison), although increased skeletal variations were observed at all doses. Dose-related teratogenic effects and increased abortion rates were reported in pigtail macaques.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no causal association have been established from these cases, 5 of the reports describe the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to fetus is not known.

##### 8.3 Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of VELTIN Gel. 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. It is not known whether tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VELTIN Gel is administered to a nursing woman.

##### 8.4 Pediatric Use

Safety and effectiveness of VELTIN Gel in pediatric patients below the age of 12 years have not been established. 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.]

#### 13 NONCLINICAL TOXICOLOGY

##### 13.1 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* reversion assay. VELTIN Gel was equivocal for clastogenic potential in the absence of metabolic activation when tested in an *in vitro* chromosomal aberration assay.

*Clindamycin:* Once daily dermal administration of 1% clindamycin as clindamycin phosphate in the VELTIN Gel vehicle (32 mg/kg/day, 13 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  $\mu$ g (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[ $\alpha$ ]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 mezeirin 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.

#### 17 PATIENT COUNSELING INFORMATION

[See FDA-approved Patient Labeling].

##### 17.1 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.

##### 17.2 Skin Irritation

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

##### 17.3 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.

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it can be billed as a 99205 E/M visit.

The second speaker, Dr. Sarah H. Springer, medical director of the International Adoption Health Services of Western Pennsylvania, recommended a wide range of lab tests, including a CBC, lead level, stool test for ova and parasite (O&P) (3), rapid plasma regain (RPR) or VDRL (Venereal Disease Research Laboratory) tests for syphilis, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HbsAb), hepatitis B core antibody (HbcAb), hepatitis C virus (HCV), HIV-1 and HIV-2, and a tuberculin skin test (PPD) or an interferon gamma release assay (IGRA) test if the child is older than 5 years of age.

These should be rechecked after 6 months, because some diseases take that long to seroconvert.

Whatever immunization records the child brings are unlikely to meet the AAP and CDC standards. "You can't take anything you get from another country at face value," said Dr. Springer, who is also with Kids Plus Pediatrics at the University of Pittsburgh Medical Center. One increasingly common exception is immunizations supervised by the U.S. State Department. Even if records do meet standards, the titers should be checked.

Otherwise, you'll often have to start from scratch, using the Red Book catch-up schedule. Note, however, that there is no pertussis coverage for children aged 7-11 years. One alternative is to use Tdap off-label. "You sometimes have to fight with the insurance company," Dr. Springer said. "They say, 'You gave it at the wrong age.' And you say, 'Would you rather pay for pertussis?'"

Among the common psychosocial issues likely to crop up in this visit are the following:

► Malnourished youngsters may hide food in their pockets, their beds, or even their cheeks. They also may eat ravenously. Dr. Schulte's advice: Let them have as much food as they want so that they will lose their fear of scarcity.

► Some children are affectionate with everyone because they are so starved for attention. They must learn to distinguish between strangers and family.

► Some are stubborn or angry, testing to see whether their new families really want to keep them. Parents must simply insist that they will always be there for these children.

► Other children may cling to one parent, crying uncontrollably if left for even a minute. Dr. Schulte advised helping these children by playing with them on the floor until they let go, then getting up to leave, promising to return and fulfilling the promise each time. Caregivers can start with separations of a couple of minutes, then gradually increase the interval.

► Adopted children may not sleep well. Because they often fear abandonment, Dr. Schulte advised against using "cry-it-out" technique to teach them good sleep patterns.

► Many children rock themselves or display other self-stimulating behavior which they embraced because they did not get any other stimulation.

► Internationally adopted kids have elevated rates of schizophrenia, bipolar disease, fetal alcohol syndrome, attention-deficit/hyperactivity disorder (ADHD), and a host of other mental illnesses.

So after that first visit, see the children often. Many will grow swiftly, catching up to their normal height, overcoming emotional challenges, and recovering from illnesses. Others will need years of special education and other support.

Dr. Springer and Dr. Schulte said they had no conflicts of interest to report, but they did discuss an unapproved/investigative use of the Tdap vaccine. ■

## VERBATIM

*'Advocacy is something we can all do. It may be something that takes only a few minutes (such as signing onto a prewritten letter to your congressman), but it is still an important contribution. It may be a larger project, but can be manageable if broken up into small discrete tasks and shared with others.'*

Dr. Lee Savio Beers, p. 54

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