

# Symptoms Over Time Suggest Chronic Lyme

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BOSTON — Persistent musculoskeletal pain, headache, fatigue, and cognitive dysfunction that occur for no apparent reason over a prolonged period of time are key elements of a clinical diagnosis of chronic Lyme disease in children, results of a retrospective study have shown.

"While there have been reports on the clinical manifestations of chronic Lyme

disease in adults, there has not been a detailing of the clinical aspects of the condition in the pediatric population, making the diagnosis especially challenging," said Sam T. Donta, M.D., in a presentation at the annual meeting of the Infectious Disease Society of America.

In an effort to identify the most telling clinical symptoms, the reliability of serologic studies, and the effects of drug therapy, Dr. Donta reviewed the clinical histories, serologies, and treatment results of

101 patients aged 2-19 years who were evaluated at Falmouth Hospital in Massachusetts for chronic Lyme disease. Tick bites occurred in 24% of the patients.

Musculoskeletal symptoms occurred in 90% of the patients, and fatigue, headache, and cognitive dysfunction were reported in 84%, 78%, and 74% of the patients, respectively. Other symptoms that occurred with some frequency included stomach pains or nausea (48%), paresthesias (46%), eye symptoms (40%), and fevers or sweats

(39%), Dr. Donta noted. Typical and atypical rashes were reported in 15% and 25% of the patients, respectively.

About 79% of the patients had other symptoms, such as dizziness, palpitations, and tremors, said Dr. Donta, who has private practices in infectious disease in Boston and Falmouth.

Bell's palsy, which is often the first neurologic symptom of Lyme disease, was reported in five patients. Of the total study population, 29 patients had undergone a brain SPECT (single photon emission computed tomography) scan, eight of which showed some changes in blood flow to various parts of the brain. Such changes, primarily to the temporal and

**The fact that there has been no detailing of the clinical aspects of chronic Lyme disease in children makes diagnosis 'especially challenging.'**

frontal lobes, are present in about 75% of patients with chronic Lyme disease, Dr. Donta stated.

Western blot serologic testing showed one or more reactions by IgM in 74% of the patients and by IgG in 82%. Enzyme immunoassay titers were positive in 65% of the patients tested. "Clearly, serologic studies can be helpful in supporting the clinical diagnosis," said Dr. Donta, but they are not definitive on their own.

All of the patients in the cohort were treated with tetracycline or a combination of a macrolide antibiotic with hydroxychloroquine over a 4- to 8-month period, and 75% of them were cured or sustained clinical improvement, Dr. Donta noted.

The key is making sure the appropriate antibiotic is used and that therapy is adhered to and sustained for a long enough period, he said. Also, "the earlier in the disease process treatment begins, the more successful it will be."

## Teens Largely Misunderstand Contraception

Many of 519 teens aged 15-17 years surveyed revealed a gap between what they think they know and what they really know about contraception.

Although teens seem to trust oral contraceptives for pregnancy prevention, nearly one in five surveyed thought newer hormonal methods, such as the patch or the ring, were not very effective at pregnancy prevention—or didn't know how effective they were.

More than one in four didn't know oral contraceptives offer no protection against sexually transmitted diseases. And a majority in the survey by the Henry J. Kaiser Family Foundation mistook the diaphragm and cervical cap as preventive of STD.

—Jennifer Silverman

**OMNICEF**  
(cefdinir)

### BRIEF SUMMARY CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

**Omnicef®** (cefdinir) capsules  
**Omnicef®** (cefdinir) for oral suspension

#### Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of OMNICEF and other antibacterial drugs, OMNICEF should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

#### CONTRAINDICATIONS

OMNICEF (cefdinir) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

#### WARNINGS

**BEFORE THERAPY WITH OMNICEF (CEFDINIR) IS INSTITUTED, CAREFUL HISTORY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFDINIR, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF CEFDINIR IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG  $\beta$ -LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFDINIR OCCURS, THE DRUG SHOULD BE DISCONTINUED. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.**

**Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefdinir, and may range in severity from mild-to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.**

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. 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*.

#### PRECAUTIONS

##### General

Prescribing OMNICEF in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other broad-spectrum antibiotics, prolonged treatment may result in the possible emergence and overgrowth of resistant organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate alternative therapy should be administered. Cefdinir, as with other broad-spectrum antimicrobials (antibiotics), should be prescribed with caution in individuals with a history of colitis. In patients with transient or persistent renal insufficiency (creatinine clearance <30 mL/min), the total daily dose of OMNICEF should be reduced because high and prolonged plasma concentrations of cefdinir can result following recommended doses.

##### Information for Patients

Patients should be counseled that antibacterial drugs including OMNICEF should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When OMNICEF is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by OMNICEF or other antibacterial drugs in the future. Antacids containing magnesium or aluminum interfere with the absorption of cefdinir. If this type of antacid is required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the antacid.

Iron supplements, including multivitamins that contain iron, interfere with the absorption of cefdinir. If iron supplements are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the supplement.

Iron-fortified infant formulas do not significantly interfere with the absorption of cefdinir. Therefore, OMNICEF for Oral Suspension can be administered with iron-fortified infant formula.

Diabetic patients and caregivers should be aware that the oral suspension contains 2.86 g of sucrose per teaspoon.

##### Drug Interactions

**Antacids:** (aluminum- or magnesium-containing): Concomitant administration of 300-mg oral cefdinir capsules with 30 mL Maalox<sup>®</sup> TC suspension reduces the rate ( $C_{max}$ ) and extent (AUC) of absorption by approximately 40%. Time to reach  $C_{max}$  is also prolonged by 1 hour. There are no significant effects on cefdinir pharmacokinetics if the antacid is administered 2 hours before or 2 hours after cefdinir. If antacids are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the antacid.

**Probenecid:** As with other  $\beta$ -lactam antibiotics, probenecid inhibits the renal excretion of cefdinir, resulting in an approximate doubling in AUC, a 54% increase in peak cefdinir plasma levels, and a 50% prolongation in the apparent elimination  $t_{1/2}$ .

**Iron Supplements and Foods Fortified With Iron:** Concomitant administration of cefdinir with a therapeutic iron supplement containing

60 mg of elemental iron (as FeSO<sub>4</sub>) or vitamins supplemented with 10 mg of elemental iron reduced extent of absorption by 80% and 31%, respectively. If iron supplements are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the supplement. The effect of foods highly fortified with elemental iron (primarily iron-fortified breakfast cereals) on cefdinir absorption has not been studied. Concomitantly administered iron-fortified infant formula (2.2 mg elemental iron/6 oz) has no significant effect on cefdinir pharmacokinetics. Therefore, OMNICEF for Oral Suspension can be administered with iron-fortified infant formula.

There have been reports of reddish stools in patients receiving cefdinir. In many cases, patients were also receiving iron-containing products. The reddish color is due to the formation of a nonabsorbable complex between cefdinir or its breakdown products and iron in the gastrointestinal tract.

#### Drug/Laboratory Test Interactions

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside, but not with those using nitroferoxydine. The administration of cefdinir may result in a false-positive reaction for glucose in urine using Clinistix<sup>®</sup>, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix<sup>®</sup> or Tes-Tape<sup>®</sup>) be used. Cephalosporins are known to occasionally induce a positive direct Coombs' test.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of cefdinir has not been evaluated. No mutagenic effects were seen in the bacterial reverse mutation assay (Ames) or point mutation assay at the hypoxanthine-guanine phosphoribosyltransferase locus (HGPRT) in V79 Chinese hamster lung cells. No clastogenic effects were observed *in vitro* in the structural chromosome aberration assay in V79 Chinese hamster lung cells or *in vivo* in the micronucleus assay in mouse bone marrow. In rats, fertility and reproductive performance were not affected by cefdinir at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on mg/m<sup>2</sup>/day).

#### Pregnancy - Teratogenic Effects

**Pregnancy Category B:** Cefdinir was not teratogenic in rats at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on mg/m<sup>2</sup>/day) or in rabbits at oral doses up to 10 mg/kg/day (0.7 times the human dose based on mg/kg/day, 0.23 times based on mg/m<sup>2</sup>/day). Maternal toxicity (decreased body weight gain) was observed in rabbits at the maximum tolerated dose of 10 mg/kg/day without adverse effects on offspring. Decreased body weight occurred in rat fetuses at  $\geq 100$  mg/kg/day, and in rat offspring at  $\geq 32$  mg/kg/day. No effects were observed on maternal reproductive parameters or offspring survival, development, behavior, or reproductive function.

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.

#### Labor and Delivery

Cefdinir has not been studied for use during labor and delivery.

#### Nursing Mothers

Following administration of single 600-mg doses, cefdinir was not detected in human breast milk.

#### Pediatric Use

Safety and efficacy in neonates and infants less than 6 months of age have not been established. Use of cefdinir for the treatment of acute maxillary sinusitis in pediatric patients (age 6 months through 12 years) is supported by evidence from adequate and well-controlled studies in adults and adolescents, the similar pathophysiology of acute sinusitis in adult and pediatric patients, and comparative pharmacokinetic data in the pediatric population.

#### Geriatric Use

Efficacy is comparable in geriatric patients and younger adults. While cefdinir has been well-tolerated in all age groups, in clinical trials geriatric patients experienced a lower rate of adverse events, including diarrhea, than younger adults. Dose adjustment in elderly patients is not necessary unless renal function is markedly compromised.

#### ADVERSE EVENTS

**Clinical Trials - OMNICEF Capsules (Adult and Adolescent Patients):** In clinical trials, 5093 adult and adolescent patients (3841 US and 1252 non-US) were treated with the recommended dose of cefdinir capsules (600 mg/day). Most adverse events were mild and self-limiting. No deaths or permanent disabilities were attributed to cefdinir. One hundred forty-seven of 5093 (3%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or definitely associated with cefdinir therapy. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea or nausea. Nineteen of 5093 (0.4%) patients were discontinued due to rash thought related to cefdinir administration.

In the US, the following adverse events were thought by investigators to be possibly, probably, or definitely related to cefdinir capsules in multiple-dose clinical trials (N=3841 cefdinir-treated patients):  
**ADVERSE EVENTS ASSOCIATED WITH CEFDINIR CAPSULES US TRIALS IN ADULT AND ADOLESCENT PATIENTS (N=3841):** Incidence  $\geq 1\%$ , Diarrhea 15%, Vaginal moniliasis 4% of women, Nausea 3%, Headache 2%, Abdominal pain 1%, Vaginitis 1% of women, Incidence <1% but  $>0.1\%$ , Rash 0.9%, Dyspepsia 0.7%, Flatulence 0.7%, Vomiting 0.7%, Abnormal stools 0.3%, Anorexia 0.3%, Constipation 0.3%, Dizziness 0.3%, Dry mouth 0.3%, Asthenia 0.2%, Insomnia 0.2%, Leukorrhea 0.2% of women, Moniliasis 0.2%, Pruritus 0.2%, Somnolence 0.2%,  
\* 1733 males, 2108 females.

The following laboratory value changes of possible clinical significance, irrespective of relationship to therapy with cefdinir, were seen during clinical trials conducted in the US: **LABORATORY VALUE CHANGES OBSERVED WITH CEFDINIR CAPSULES US TRIALS IN ADULT AND ADOLESCENT PATIENTS (N=3841):** Incidence  $\geq 1\%$ ,  $\uparrow$ Urine leukocytes 2%,  $\uparrow$ Urine protein 2%,  $\uparrow$ Gamagamma-glutamyltransferase 1%,  $\uparrow$ Lymphocytes,  $\uparrow$ Thrombocytes 1%, 0.2%,  $\uparrow$ Microrhematuria 1%, Incidence <1% but  $>0.1\%$ ,  $\uparrow$ Glucose 0.9%,  $\uparrow$ Urine glucose 0.9%,  $\uparrow$ White blood cells,  $\uparrow$ White blood cells 0.9%, 0.7%,  $\uparrow$ Alkaline aminotransferase (ALT) 0.7%,  $\uparrow$ Eosinophils 0.7%,  $\uparrow$ Urine specific gravity,  $\uparrow$ Urine specific gravity 0.6%, 0.2%,  $\uparrow$ Bicarbonate 0.6%,  $\uparrow$ Phosphorus,  $\uparrow$ Phosphorus 0.6%, 0.3%,  $\uparrow$ Aspartate aminotransferase (AST) 0.4%,  $\uparrow$ Alkaline phosphatase 0.3%,  $\uparrow$ Blood urea nitrogen (BUN) 0.3%,  $\uparrow$ Hemoglobin 0.3%,  $\uparrow$ Polymorphonuclear (PMNs),  $\uparrow$ PMNs 0.3%, 0.2%,  $\uparrow$ Bilirubin 0.2%,  $\uparrow$ Lactate dehydrogenase 0.2%,  $\uparrow$ Platelets 0.2%,  $\uparrow$ Potassium 0.2%,  $\uparrow$ Urine pH 0.2%,  
\* N=3841 for these parameters

#### Clinical Trials - OMNICEF for Oral Suspension (Pediatric Patients):

In clinical trials, 2289 pediatric patients (1783 US and 506 non-US) were treated with the recommended dose of cefdinir suspension (14 mg/kg/day). Most adverse events were mild and self-limiting. No deaths or permanent disabilities were attributed to cefdinir. Forty of 2289 (2%) patients discontinued medication due to adverse events considered by the investigators to be possibly, probably, or definitely associated with cefdinir therapy. Discontinuations were primarily for gastrointestinal disturbances, usually diarrhea. Five of 2289 (0.2%) patients were discontinued due to rash thought related to cefdinir administration.

In the US, the following adverse events were thought by investigators to be possibly, probably, or definitely related to cefdinir suspension in multiple-dose clinical trials (N=1783 cefdinir-treated patients):

**ADVERSE EVENTS ASSOCIATED WITH CEFDINIR SUSPENSION US TRIALS IN PEDIATRIC PATIENTS (N=1783):** Incidence  $\geq 1\%$ , Diarrhea 8%, Rash 3%, Vomiting 1%, Incidence <1% but  $>0.1\%$ , Cutaneous moniliasis 0.9%, Abdominal pain 0.8%, Leukopenia 0.3%, Vaginal moniliasis 0.3% of girls, Vaginitis 0.3% of girls, Abnormal stools 0.2%, Dyspepsia 0.2%, Hyperkinesia 0.2%, Increased AST 0.2%, Maculopapular rash 0.2%, Nausea 0.2%,  $\uparrow$ PTT males, 806 females.  
Laboratory changes were occasionally reported as adverse events.

**NOTE:** In both cefdinir- and control-treated patients, rates of diarrhea and rash were higher in the youngest pediatric patients. The incidence of diarrhea in cefdinir-treated patients  $\leq 2$  years of age was 17% (95/557) compared with 4% (51/1226) in those  $>2$  years old. The incidence of rash (primarily diaper rash in the younger patients) was 8% (43/557) in patients  $\leq 2$  years of age compared with 1% (8/1226) in those  $>2$  years old. The following laboratory value changes of possible clinical significance, irrespective of relationship to therapy with cefdinir, were seen during clinical trials conducted in the US:

**LABORATORY VALUE CHANGES OF POSSIBLE CLINICAL SIGNIFICANCE OBSERVED WITH CEFDINIR SUSPENSION US TRIALS IN PEDIATRIC PATIENTS (N=1783):** Incidence  $>1\%$  Lymphocytes, 2%, 0.8%,  $\uparrow$ Lymphocytes 1%,  $\uparrow$ Alkaline phosphatase 1%,  $\uparrow$ Bicarbonate 1%,  $\uparrow$ Eosinophils 1%,  $\uparrow$ Lactate dehydrogenase 1%,  $\uparrow$ Platelets 1%,  $\uparrow$ PMNs,  $\uparrow$ PMNs 1%,  $\uparrow$ Urine protein 1%, Incidence <1% but  $>0.1\%$ ,  $\uparrow$ Phosphorus,  $\uparrow$ Phosphorus 0.9%, 0.4%,  $\uparrow$ Urine pH 0.8%,  $\uparrow$ White blood cells,  $\uparrow$ White blood cells 0.7%, 0.3%,  $\uparrow$ Calcium 0.5%,  $\uparrow$ Hemoglobin 0.5%,  $\uparrow$ Urine leukocytes 0.5%,  $\uparrow$ Monocytes 0.4%,  $\uparrow$ AST 0.3%,  $\uparrow$ Potassium 0.3%,  $\uparrow$ Urine specific gravity,  $\uparrow$ Urine specific gravity 0.3%, 0.1%,  $\uparrow$ Hematocrit 0.2%,  $\uparrow$ 1387 for these parameters

#### Postmarketing Experience

The following adverse experiences and altered laboratory tests, regardless of their relationship to cefdinir, have been reported during extensive postmarketing experience, beginning with approval in Japan in 1991: Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, erythema nodosum, conjunctivitis, stomatitis, acute hepatitis, cholestasis, fulminant hepatitis, hepatic failure, jaundice, increased amylase, shock, anaphylaxis, facial and laryngeal edema, feeling of suffocation, acute enterocolitis, bloody diarrhea, hemorrhagic colitis, melena, pseudomembranous colitis, pancytopenia, granulocytopenia, leukopenia, thrombocytopenia, idiopathic thrombocytopenic purpura, hemolytic anemia, acute respiratory failure, asthmatic attack, drug-induced pneumonia, eosinophilic pneumonia, idiopathic interstitial pneumonia, fever, acute renal failure, nephropathy, bleeding tendency, coagulation disorder, disseminated intravascular coagulation, upper GI bleed, peptic ulcer, ileus, loss of consciousness, allergic vasculitis, possible cefdinir-diclofenac interaction, cardiac failure, chest pain, myocardial infarction, hypertension, involuntary movements, and rhabdomyolysis.

#### Cephalosporin Class Adverse Events

The following adverse events and altered laboratory tests have been reported for cephalosporin-class antibiotics in general:  
Allergic reactions, anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, false-positive test for urinary glucose, neutropenia, pancytopenia, and agranulocytosis. Pseudomembranous colitis symptoms may begin during or after antibiotic treatment (see WARNINGS).

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see OVERDOSAGE). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

#### OVERDOSAGE

Information on cefdinir overdosage in humans is not available. In acute rodent toxicity studies, a single oral 5600-mg/kg dose produced no adverse effects. Toxic signs and symptoms following overdosage with other  $\beta$ -lactam antibiotics have included nausea, vomiting, epigastric distress, diarrhea, and convulsions. Hemodialysis removes cefdinir from the body. This may be useful in the event of a serious toxic reaction from overdosage, particularly if renal function is compromised.

#### Rx only

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