

# Invasive GAS Contacts May Not Need Prophylaxis

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CHICAGO — Offering prophylaxis to all household contacts of patients with invasive group A streptococcal disease may not be cost effective, according to findings from an epidemiologic study presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy.

The Centers for Disease Control and Prevention recommends that chemopro-

phylaxis be given only to household contacts at increased risk of group A streptococcus (GAS) disease. In the United Kingdom, chemoprophylaxis is routinely given to maternal or neonatal index cases, Dr. Stephanie W. Smith explained.

In Canada, however, where the study was conducted, guidelines recommend that if a household member has more than 4 hours of contact with the index case in the 7 days prior to onset of illness, then that person should be offered chemoprophylaxis.

In a study aimed at describing the epidemiology of household clusters of invasive GAS, Dr. Smith and her colleagues analyzed data on 12 million people in Ontario.

"In looking at the issue of prophylaxis, over the period from 1992 to 2001 we had over 2,000 cases of invasive GAS, and we had another 982 cases from 2001 to 2004, of which 610 were from the population base of 4 million people in the Toronto area," said Dr. Smith of the division of in-

fectious diseases at the University of Alberta in Edmonton.

The incidence of invasive GAS ranged from 1.5 to 3.4 per 100,000 people; data regarding prophylaxis of household contacts were available for 968 cases, Dr. Smith said.

Results from previous population-based studies suggest that the worldwide annual incidence of invasive GAS is between 1.25 and 6 per 100,000, she explained.

The researchers identified eight household clusters, each consisting of two cases of GAS disease, including four husband-wife pairs, one brother-brother pair, two mother-son pairs, and one father-daughter pair, she said, adding that the average age of secondary cases was 54 years (range 29-83 years).

Risk factors for sporadic disease include residence in a nursing home, extremes of age, recent varicella infection, HIV, diabetes, heart disease, cancer, use of high-dose steroids, and intravenous drug use.

In this study, only two of the secondary cases had risk factors for sporadic GAS disease, Dr. Smith said at the meeting, which was sponsored by the American Society for Microbiology.

All cases had bacteremia, including one pair with necrotizing fasciitis, one pair with prepatellar bursitis, three pairs with soft tissue infection, and one pair with soft tissue infection and peritonitis.

None of the secondary cases received chemoprophylaxis, and all primary and secondary cases within these eight households survived, Dr. Smith said, adding that of the 968 cases with documentation regarding chemoprophylaxis, only 28% of household contacts received it, suggesting a low adherence to Canadian guidelines.

Prophylaxis may have prevented several secondary cases, "but we still think our data are reasonably robust and represent the largest series of household clusters," Dr. Smith said in an interview.

"If we assume 100% efficacy of prophylaxis, based on our secondary infection rate in Ontario, we would have to treat 806 household contacts to prevent one case of invasive disease at an estimated cost of \$33,000 per case prevented," she said, adding that a formal cost-effectiveness analysis was not completed.

Invasive group A streptococcus can cause a variety of invasive syndromes, including necrotizing fasciitis, toxic shock syndrome, pneumonia, and bacteremia. The overall mortality rate of between 10% and 20% is highest among the elderly, the very young, and those who have had a recent varicella infection or who have other comorbidities.

"We think the secondary attack rate is a bit higher than the sporadic rate, but [it] is definitely lower than what we found in the initial Ontario data, and the most common risk factor does seem to be advanced age," Dr. Smith said, adding that offering all household contacts chemoprophylaxis may not be cost-effective given the combined public health and antibiotic costs.

"However, offering prophylaxis to those at increased risk for sporadic disease or for severe disease ... may be the most cost-effective approach," she said. ■

Depression	2	2	2	2	2	2
<b>Respiratory, Thoracic and Mediastinal Disorders</b>						
Pharyngolaryngeal pain	2	1	3	3	2	2

\*PGB: pregabalin

**Other Adverse Reactions Observed During the Clinical Studies of LYRICA** Following is a list of treatment-emergent adverse reactions reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse reactions are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the *Warnings and Precautions* section. Body as a Whole — *Frequent*: Abdominal pain, Allergic reaction, Fever, *Infrequent*: Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction, Suicide attempt, *Rare*: Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional Injury, Retroperitoneal Fibrosis, Shock, Suicide. Cardiovascular System — *Infrequent*: Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope, *Rare*: ST Depressed, Ventricular Fibrillation. Digestive System — *Frequent*: Gastroenteritis, Increased appetite, *Infrequent*: Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare*: Aphthous stomatitis, Esophageal Ulcer, Peritoneal abscess. Hemic and Lymphatic System — *Frequent*: Erythema; *Infrequent*: Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare*: Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocytopenia. Metabolic and Nutritional Disorders — *Rare*: Glucose Tolerance Decreased, Urate Crystalluria. Musculoskeletal System — *Frequent*: Arthralgia, Leg cramps, Myalgia, Myasthenia; *Infrequent*: Arthritis; *Rare*: Chondrodystrophy, Generalized Spasm. Nervous System — *Frequent*: Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching, *Infrequent*: Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia, *Rare*: Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillaing-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus. Respiratory System — *Rare*: Apnea, Atelectasis, Bronchiolitis, Hiccups, Laryngismus, Lung edema, Lung fibrosis, Yawn. Skin and Appendages — *Frequent*: Pruritus, *Infrequent*: Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare*: Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Nail Disorder, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule. Special senses — *Frequent*: Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent*: Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare*: Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis. Urogenital System — *Frequent*: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence; *Infrequent*: Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, Urine abnormality; *Rare*: Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis, Ovarian disorder, Pyelonephritis. Comparison of Gender and Race The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race. **Post-marketing Experience** The following adverse reactions have been identified during postapproval use of LYRICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Nervous System Disorders — Headache. Gastrointestinal Disorders — Nausea, Diarrhea

## USE IN SPECIFIC POPULATIONS

**Pregnancy** Pregnancy Category C. Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC)  $\geq$  5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at  $\geq$ 1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established. When pregnant rabbits were given LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD. In a study in which female rats were dosed with LYRICA (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at  $\geq$ 100 mg/kg and offspring survival was decreased at  $\geq$ 250 mg/kg. The effect on offspring survival was pronounced at doses  $\geq$ 1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at  $\geq$ 250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD. There are no adequate and well-controlled studies in pregnant women. LYRICA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effects of LYRICA on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures  $\geq$  50 times the mean human exposure (AUC<sub>0-24</sub> of 123  $\mu$ g-hr/mL) at the maximum recommended clinical dose of 600 mg/day. **Nursing Mothers** It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, 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** The safety and efficacy of pregabalin in pediatric patients have not been established. In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses  $\geq$  50 mg/kg. The neurobehavioral changes of acoustic startle persisted

at  $\geq$  250 mg/kg and locomotor activity and water maze performance at  $\geq$  500 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established. **Geriatric Use** In controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 246 patients were 65 to 74 years of age, and 73 patients were 75 years of age or older. In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older. In controlled clinical studies of LYRICA in epilepsy, there were only 10 patients 65 to 74 years of age, and 2 patients who were 75 years of age or older. No overall differences in safety and efficacy were observed between these patients and younger patients. In controlled clinical studies of LYRICA in fibromyalgia, 106 patients were 65 years of age or older. Although the adverse reaction profile was similar between the two age groups, the following neurological adverse reactions were more frequent in patients 65 years of age or older: dizziness, vision blurred, balance disorder, tremor, confusional state, coordination abnormal, and lethargy. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment [see *Dosage and Administration*].

## DRUG ABUSE AND DEPENDENCE

**Controlled Substance** LYRICA is a Schedule V controlled substance. LYRICA is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior). **Abuse** In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, LYRICA (450mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30mg, single dose). In controlled clinical studies in over 5500 patients, 4% of LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. **Dependence** In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache or diarrhea [see *Warnings and Precautions*], suggestive of physical dependence.

## OVERDOSAGE

**Signs, Symptoms and Laboratory Findings of Acute Overdose in Humans** There is limited experience with overdose of LYRICA. The highest reported accidental overdose of LYRICA during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse reactions experienced by patients exposed to higher doses ( $\geq$ 900 mg) were not clinically different from those of patients administered recommended doses of LYRICA. **Treatment or Management of Overdose** There is no specific antidote for overdose with LYRICA. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with LYRICA. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

## PATIENT COUNSELING INFORMATION

**Patient Package Insert** Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA. **Angioedema** Patients should be advised that LYRICA may cause angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Patients should be instructed to discontinue LYRICA and immediately seek medical care if they experience these symptoms [see *Warnings and Precautions*]. **Hypersensitivity** Patients should be advised that LYRICA has been associated with hypersensitivity reactions such as wheezing, dyspnea, rash, hives, and blisters. Patients should be instructed to discontinue LYRICA and immediately seek medical care if they experience these symptoms [see *Warnings and Precautions*]. **Dizziness and Somnolence** Patients should be counseled that LYRICA may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on LYRICA to gauge whether or not it affects their mental, visual, and/or motor performance adversely [see *Warnings and Precautions*]. **Weight Gain and Edema** Patients should be counseled that LYRICA may cause edema and weight gain. Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure [see *Warnings and Precautions*]. **Abrupt or Rapid Discontinuation** Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea [see *Warnings and Precautions*]. **Ophthalmological Effects** Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician [see *Warnings and Precautions*]. **Creatine Kinase Elevations** Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever [see *Warnings and Precautions*]. **CNS Depressants** Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence. **Alcohol** Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedating effects of alcohol. **Use in Pregnancy** Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy [see *Use in Specific Populations*]. **Male Fertility** Men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain. **Dermatopathy** Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials.



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