

# QUIXIN®

(levofloxacin ophthalmic solution) 0.5%

## BRIEF SUMMARY

### DESCRIPTION

QUIXIN® (levofloxacin ophthalmic solution) 0.5% is a sterile topical ophthalmic solution. Levofloxacin is a fluoroquinolone antibacterial active against a broad spectrum of Gram-positive and Gram-negative ocular pathogens. Levofloxacin is the pure (-)-(-)-enantiomer of the racemic drug substance, ofloxacin. It is more soluble in water at neutral pH than ofloxacin.

QUIXIN® solution is isotonic and formulated at pH 6.5 with an osmolality of approximately 300 mOsm/kg. Levofloxacin is a fluorinated 4-quinolone containing a six-member (pyridobenzoxazine) ring from positions 1 to 8 of the basic ring structure.

**Clinical Studies:** In randomized, double-masked, multicenter controlled clinical trials where patients were dosed for 5 days, QUIXIN® demonstrated clinical cures in 79% of patients treated for bacterial conjunctivitis on the final study visit day (day 6-10). Microbial outcomes for the same clinical trials demonstrated an eradication rate for presumed pathogens of 90%.

### INDICATIONS AND USAGE

QUIXIN® solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

#### AEROBIC GRAM-POSITIVE MICROORGANISMS

*Corynebacterium* species\*  
*Staphylococcus aureus*  
*Staphylococcus epidermidis*  
*Streptococcus pneumoniae*  
*Streptococcus* (Groups C/F)  
*Streptococcus* (Group G)  
Viridans group streptococci

\*Efficacy for this organism was studied in fewer than 10 infections.

#### AEROBIC GRAM-NEGATIVE MICROORGANISMS

*Acinetobacter lwoffii*\*  
*Haemophilus influenzae*  
*Serratia marcescens*\*

### CONTRAINDICATIONS

QUIXIN® solution is contraindicated in patients with a history of hypersensitivity to levofloxacin, to other quinolones, or to any of the components in this medication.

### WARNINGS

#### NOT FOR INJECTION.

QUIXIN® solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

In patients receiving systemic quinolones, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to levofloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

### PRECAUTIONS

**General:** As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

**Information for Patients:** Avoid contaminating the applicator tip with material from the eye, fingers or other source. Systemic quinolones have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

**Drug Interactions:** Specific drug interaction studies have not been conducted with QUIXIN®. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, and enhance the effects of the oral anticoagulant warfarin and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving systemic cyclosporine concomitantly.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a long term carcinogenicity study in rats, levofloxacin exhibited no carcinogenic or tumorigenic potential following daily dietary administration for 2 years; the highest dose (100 mg/kg/day) was 875 times the highest recommended human ophthalmic dose.

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (*S. typhimurium* and *E. coli*), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the *in vivo* mouse sister chromatid exchange assay. It was positive in the *in vitro* chromosomal aberration (CHL cell line) and *in vitro* sister chromatid exchange (CHL/II cell line) assays.

Levofloxacin caused no impairment of fertility or reproduction in rats at oral doses as high as 360 mg/kg/day, corresponding to 3,150 times the highest recommended human ophthalmic dose.

**Pregnancy: Teratogenic Effects. Pregnancy Category C:** Levofloxacin at oral doses of 810 mg/kg/day in rats, which corresponds to approximately 7,000 times the highest recommended human ophthalmic dose, caused decreased fetal body weight and increased fetal mortality.

No teratogenic effect was observed when rabbits were dosed orally as high as 50 mg/kg/day, which corresponds to approximately 400 times the highest recommended maximum human ophthalmic dose, or when dosed intravenously as high as 25 mg/kg/day, corresponding to approximately 200 times the highest recommended human ophthalmic dose.

There are, however, no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin is excreted in human milk. Caution should be exercised when QUIXIN® is administered to a nursing mother.

**Pediatric Use:** Safety and effectiveness in infants below the age of one year have not been established. Oral administration of quinolones has been shown to cause arthropathy in immature animals. There is no evidence that the ophthalmic administration of levofloxacin has any effect on weight bearing joints.

**Geriatric Use:** No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

### ADVERSE REACTIONS

The most frequently reported adverse events in the overall study population were transient decreased vision, fever, foreign body sensation, headache, transient ocular burning, ocular pain or discomfort, pharyngitis and photophobia. These events occurred in approximately 1-3% of patients. Other reported reactions occurring in less than 1% of patients included allergic reactions, lid edema, ocular dryness, and ocular itching.

Rx only

**Manufactured by:**  
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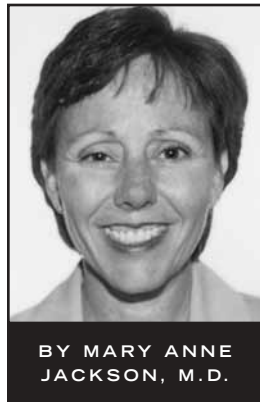
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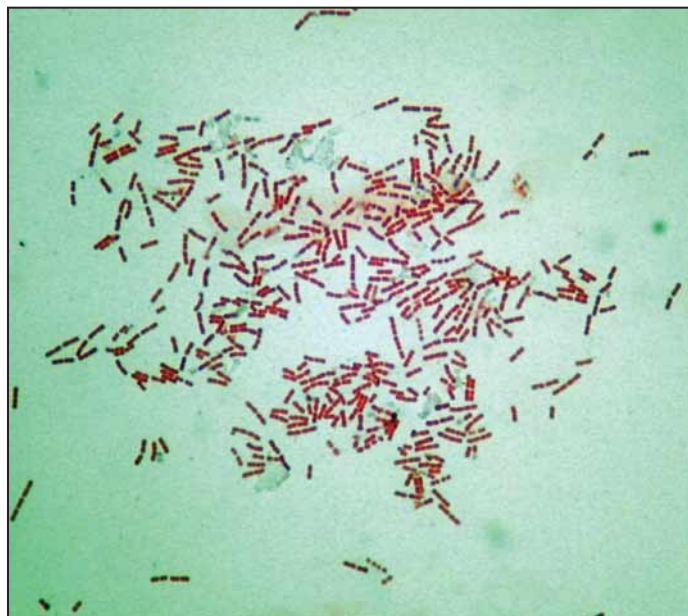


BY MARY ANNE JACKSON, M.D.

tations in our institution. Early diagnosis, prompt surgical drainage, and appropriate antimicrobial therapy remain the keys to good outcome. While the clinical manifestations of these infections haven't changed over the years, the microbiologic etiologies have, and this has impacted therapeutic decision making.

Staphylococcal infection remains the most common cause of skeletal infection overall. In recent years, as methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged, clindamycin has become a common empiric antimicrobial choice for such cases. However, this may not be a good choice for therapy for some children with skeletal infection.

Once considered an unusual cause of pediatric infection, *Kingella kingae* has



An example of a typical Gram stain of organisms from a *Kingella kingae* colony is shown.

emerged as potentially the No. 1 cause of septic arthritis in the child younger than 24 months of age. This fastidious organism, which is often resistant to clindamycin, colonizes the oropharynx of approximately 15% of healthy toddler children. The problem is, it is difficult to grow on culture, requiring an enhanced isolation methodology and a little longer than normal (4.4 days) to grow. Knowing when to think about *K. kingae* as a potential pathogen should help you provide successful treatment for such children.

Consider the typical case in which a previously healthy and fully immunized child toddler with a recent upper respiratory infection (URI) presents in your office with a high spiking fever and irritability. History reveals no ill contacts, pets, or travel, and you cannot localize a focus for fever or fussiness on examination.

The next day, the child is limping. At this point, further evaluation is warranted and you consider the diagnosis of sep-

## ID CONSULT

# Kingella kingae Emerging

Skeletal infection has always been among the top five reasons for inpatient pediatric infectious disease consul-

tic arthritis, keeping in mind that it is a medical and surgical emergency. In the febrile limping toddler with presumed septic arthritis, immediate evaluation by an orthopedic surgeon is necessary. Joint drainage is promptly performed.

What tip-offs might suggest to you that *K. kingae* should be considered as a potential pathogen, and how might this impact your therapeutic decision making?

For the most part, this organism is an important cause of skeletal infection only in those less than 2

years of age. Other information that may be helpful includes the fact that concomitant URI or stomatitis occurs frequently in such patients (over half in one study), suggesting a respiratory or buccal source for the infection. And this organism has a predilection for ankle involvement in cases of arthritis and calcaneal involvement in bone infection.

Keeping this in mind, since *K. kingae* is

extremely hard to grow on culture, you should alert your surgeon and microbiology laboratory. In addition to routine cultures, ask your orthopedic surgeon to place some of the purulent fluid into a blood culture bottle, in addition to plating for routine culture. Over a decade ago, physicians were alerted to the importance of using BACTEC blood culture bottles to isolate *K. kingae* in toddlers with skeletal infection (J. Clin. Microbiol. 1992;30:1278-81).

The investigators analyzed culture records for the 1988-1991 period and compared the performance of routine culture versus use of blood culture bottle for the recovery of pathogens. A diagnostic joint tap was performed in 216 children. Of those, 63 specimens grew significant organisms. Both methods were comparable for recovery of usual pathogens, but *K. kingae* isolates were detected by the BACTEC system only, in 13 of 14 specimens.

Just how often *K. kingae* is the culprit in infant septic arthritis is not completely clear since many centers have not routinely used the above technique to enhance growth.

In a study conducted in Atlanta between 1990 and 1995, where joint aspirates were inoculated into thioglycolate broth, rather than blood culture, gram-positive bacteria were identified in 47 of 60 children (78%) younger than 3 years of age with culture-

positive hematogenous septic arthritis and acute or subacute osteomyelitis, while gram-negative organisms were identified in 13 (22%). Of those, *K. kingae* was cultured in 10 (17%); all such cases occurred in children between the ages of 10.5 and 23.5 months. (J. Pediatr. Orthop. 1998;18:262-7).

Now comes information that implicates *K. kingae* in a cluster of skeletal infection in one day care center in Minnesota. Three cases occurred among children aged 17-21 months attending the same toddler classroom. Within the same week, all affected children had onset of fever, and antalgic gait. They all had preceding or concurrent upper respiratory illness. *K. kingae* was isolated from clinical specimens.

For physicians who have been practicing long enough to remember the *Haemophilus influenzae* type b era, this may seem familiar.

Before the Hib vaccine became widely used, *H. influenzae* type b was recognized as the etiologic agent in 80% of septic arthritis cases in children less than 2 years of age, and day care center outbreaks were notable.

A colonization study was performed in response to the Minnesota outbreak. Published in Pediatrics in August 2005, the investigators demonstrated that 13% of children at the index day care center (and 45% in the room where the cluster occurred) were colonized in the nasopharynx with *K. kingae*. Interestingly, no day care center staff or children less than 16 months old were colonized. They compared the nasopharyngeal colonization results with a control day care center. Similarly, 16% of toddler age children were colonized. (Pediatrics 2005;116:e206-13).

In the pre-Hib vaccine era, we routinely used to use rifampin to eradicate Hib carriage among children in day care. Rifampin was used to attempt decolonization of children in the outbreak but proved to be only moderately effective: three of nine children who took rifampin remained positive on reculture 10-14 days later.

As practitioners recognize the importance of recognizing *K. kingae* as a pathogen in the infant with skeletal infection (and others are noting the emergence of clindamycin-resistant MRSA), clinical decision making in cases of pediatric skeletal infection are becoming increasingly difficult.

A collaborative approach with you, your infectious disease specialist, and orthopedic surgeon that focuses on early diagnosis, pathogen isolation, prompt surgical drainage, and appropriate antimicrobial therapy should allow for the best outcomes.

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