

In-Office Diagnostics Can Improve Clinical Care

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BOSTON — Rapid in-office testing for infectious diseases can help physicians get the right drug on board as quickly as possible, and cut down on unnecessary testing and inappropriate antibiotics. “I really do believe that having the diagnosis in real time can affect clinical decision making,” Dr. Leonard Krilov said at the annual meeting of the American

Academy of Pediatrics. “For instance, with rapid influenza testing, it’s been shown that doctors who have a confirmed diagnosis from a rapid flu test order less unnecessary tests, fewer radiographs, and give out less antibiotics and more antiviral drugs.” The only diagnostic tests approved for use in the office setting are those that have been waived by the Clinical Laboratory Improvement Amendments of 1988 (CLIA) law.

Vigamox[®]
(moxifloxacin hydrochloride ophthalmic solution) 0.5% as base
DESCRIPTION: VIGAMOX[®] (moxifloxacin HCl ophthalmic solution) 0.5% is a sterile ophthalmic solution. It is an 8-methoxy fluoroquinolone anti-infective for topical ophthalmic use.
CLINICAL PHARMACOLOGY:
Microbiology: The following *in vitro* data are also available, **but their clinical significance in ophthalmic infections is unknown.** The safety and effectiveness of VIGAMOX[®] solution in treating ophthalmological infections due to these microorganisms have not been established in adequate and well-controlled trials.
The following organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. The list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections. Moxifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 µg/ml or less (systemic susceptible breakpoint) against most (≥ 90%) strains of the following ocular pathogens.
Aerobic Gram-positive microorganisms:

<i>Listeria monocytogenes</i>	<i>Streptococcus mitis</i>
<i>Staphylococcus saprophyticus</i>	<i>Streptococcus pyogenes</i>
<i>Streptococcus agalactiae</i>	<i>Streptococcus</i> Group C, G and F

Aerobic Gram-negative microorganisms:

<i>Acinetobacter baumannii</i>	<i>Klebsiella pneumoniae</i>
<i>Acinetobacter calcoaceticus</i>	<i>Moraxella catarrhalis</i>
<i>Citrobacter freundii</i>	<i>Morganella morganii</i>
<i>Citrobacter koseri</i>	<i>Neisseria gonorrhoeae</i>
<i>Enterobacter aerogenes</i>	<i>Proteus mirabilis</i>
<i>Enterobacter cloacae</i>	<i>Proteus vulgaris</i>
<i>Escherichia coli</i>	<i>Pseudomonas stutzeri</i>
<i>Klebsiella oxytoca</i>	

Anaerobic microorganisms:

<i>Clostridium perfringens</i>	<i>Prevotella</i> species
<i>Fusobacterium</i> species	<i>Propionibacterium acnes</i>

Other microorganisms:

<i>Chlamydia pneumoniae</i>	<i>Mycobacterium marinum</i>
<i>Legionella pneumophila</i>	<i>Mycoplasma pneumoniae</i>
<i>Mycobacterium avium</i>	

Clinical Studies:
In two randomized, double-masked, multicenter, controlled clinical trials in which patients were dosed 3 times a day for 4 days, VIGAMOX[®] solution produced clinical cures on day 5-6 in 66% to 69% of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of the baseline pathogens ranged from 84% to 94%. Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.
INDICATIONS AND USAGE: VIGAMOX[®] solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:
Aerobic Gram-positive microorganisms:

<i>Corynebacterium</i> species*	<i>Staphylococcus hominis</i>
<i>Micrococcus luteus</i> *	<i>Staphylococcus warneri</i> *
<i>Staphylococcus aureus</i>	<i>Streptococcus pneumoniae</i>
<i>Staphylococcus epidermidis</i>	<i>Streptococcus viridans</i> group
<i>Staphylococcus haemolyticus</i>	

Aerobic Gram-negative microorganisms:

<i>Acinetobacter lwoffii</i> *	<i>Haemophilus parainfluenzae</i> *
<i>Haemophilus influenzae</i>	

Other microorganisms:
Chlamydia trachomatis
*Efficacy for this organism was studied in fewer than 10 infections.
CONTRAINDICATIONS: VIGAMOX[®] solution is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, or to any of the components in this medication.
WARNINGS:
NOT FOR INJECTION.
VIGAMOX[®] solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.
In patients receiving systemically administered quinolones, including moxifloxacin, 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 moxifloxacin occurs, discontinue use of 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.

Systemically administered quinolones including moxifloxacin 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: Drug-drug interaction studies have not been conducted with VIGAMOX[®] solution. *In vitro* studies indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2 indicating that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. However, in an accelerated study with initiators and promoters, moxifloxacin was not carcinogenic in rats following up to 38 weeks of oral dosing at 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose for a 50 kg person, on a mg/kg basis).

Moxifloxacin was not mutagenic in four bacterial strains used in the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity *in vivo* in a micronucleus test or a dominant lethal test in mice.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 21,700 times the highest recommended total daily human ophthalmic dose. At 500 mg/kg orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

Pregnancy: Teratogenic Effects.
Pregnancy Category C: Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose); however, decreased fetal body weights and slightly delayed fetal skeletal development were observed. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (approximately 4,300 times the highest recommended total daily human ophthalmic dose). An increased incidence of smaller fetuses was observed at 100 mg/kg/day.

Since there are no adequate and well-controlled studies in pregnant women, VIGAMOX[®] solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Moxifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when VIGAMOX[®] solution is administered to a nursing mother.

Pediatric Use: The safety and effectiveness of VIGAMOX[®] solution in infants below 1 year of age have not been established.

There is no evidence that the ophthalmic administration of VIGAMOX[®] solution has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS:
The most frequently reported ocular adverse events were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, and tearing. These events occurred in approximately 1-6% of patients.

Nonocular adverse events reported at a rate of 1-4% were fever, increased cough, infection, otitis media, pharyngitis, rash, and rhinitis.

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References:
1. Lichtenstein SJ, Dorfman M, Kennedy R, Stroman D. Controlling contagious bacterial conjunctivitis. *J Pediatr Ophthalmol Strabismus*. 2006;43:19-26.
2. Data on file. Alcon Laboratories, Inc.

Waived tests are defined as simple laboratory examinations and procedures that are cleared by the Food and Drug Administration for home use; employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible; and pose no reasonable risk of harm to the patient if it’s performed incorrectly.

The most common in-office tests for infectious diseases include those for group A streptococcus (GAS), influenza, respiratory syncytial virus (RSV), mononucleosis, and human immunodeficiency virus (HIV), said Dr. Krilov, chief of pediatric infectious diseases at Winthrop University Hospital, Mineola, N.Y.

There are 35 CLIA-waived tests for GAS, with varying ranges of sensitivity and specificity.

“Overall, the tests are very specific, ranging from 85% to 100%, but the concern is that the sensitivity is quite variable and can be as low as 62%,” Dr. Krilov reported.

Because of this, a negative test always requires a backup throat culture for confirmation. On the other hand, “If you get a positive test, you can believe it. There’s no need for a culture,” he said.

However, even a positive test doesn’t mean that the presenting symptoms are because of GAS pharyngitis.

“Recovery of group A strep from the pharynx doesn’t necessarily distinguish true infection from carriers who might happen to have a coincidental viral pharyngitis. You can’t completely rely on the test—you have to be able to interpret the clinical picture as well,” Dr. Krilov explained.

Of the 15 rapid influenza tests available, 3 are waived for office use; they all yield results in about 30 minutes. Although they are highly specific (90%-95%), the sensitivity isn’t great (70%-75%), Dr. Krilov said.

Because of this, he continued, “successfully using these is somewhat dependent on the time of year and the likelihood of influenza infection in your community. False positives and true negatives are more likely if prevalence is low, but false negatives and true positives are more likely in the midst of an epidemic. But in the right time of winter, with the right clinical picture, a positive test is both believable and important.”

Accuracy also depends on when during the course of illness testing occurs. In children, most of the viral shedding occurs in the first 48 hours.

The quality of the specimen is very important as well, Dr. Krilov noted. “The more secretions you get, the more cell material you get, so a nasal wash or aspirate is probably better than a nasopharyngeal swab.”

Especially in light of the continued emergence of antibiotic-resistant bacteria, an early, certain diagnosis of viral illness can significantly decrease inappropriate

antibiotic prescribing, Dr. Krilov said. A 2003 study enrolled 391 patients with symptoms of influenza; all had a rapid flu test done in the hospital. Half of the referring physicians were given the results; these doctors ordered significantly fewer lab tests and x-rays and prescribed significantly fewer antibiotics than physicians who didn’t know the diagnosis.

Additionally, Dr. Krilov reported, treatment costs and hospital length of stay were significantly lower for patients whose diagnosis was known; the rate of antiviral prescriptions given to these patients also was significantly higher than for those whose diagnosis was not known (Pediatrics 2003;112:363-7).

Most testing for RSV is done in the hospital, but one test is available for office use. It detects RSV fusion protein, and results are available in 15 minutes. The kit has a sensitivity of up to 88% and specificity of up to 100%.

“Again, if it’s winter and RSV is in the community, you can believe a positive result,” he said. “It might be useful in how you monitor the patient, and it’s very helpful in preventing unnecessary antibiotic use. But I’m not sure it helps much with family education or helps you make any decision about admission.”

Monospot is the only CLIA-waived test for mononucleosis. Again, accuracy depends on timing, Dr. Krilov said. “A negative test in the first week of illness does not mean they don’t have the disease. Typically it isn’t until the second week of illness that the heterophile antibodies are made, and they can persist for 6 months or more. So using this test to follow the course of disease, or as a way of determining when the kids can go back to school and sports, is not worthwhile. “

Children younger than 6 years may not even make the heterophile antibodies, so a negative test on a young child shouldn’t affect clinical decision-making, Dr. Krilov said. “The antibodies are detected in up to 85% of older kids and adolescents, but [in] 40% or less of those younger than 4 years. If you have a patient of the appropriate age and the appropriate symptoms, and the test is negative, you can treat it as early disease and test again in 1-2 weeks. Or you have the option of sending to the lab for specific serology.”

Dr. Krilov also touched on the issue of in-office HIV testing. Two CLIA-waived kits are available and give results in 20 minutes. “I think it’s useful in some clinical settings, since it allows more people to be tested. At present, we estimate that up to 280,000 people in the U.S. are unaware that they have an HIV infection. The bad news is they don’t give a complete diagnostics, so a positive test always has to be confirmed by the Western blot analysis, and a false positive can create a lot of anxiety. The other part of HIV testing is, if you do the test, it needs to be done in conjunction with counseling and hooking patients into appropriate follow-up.” ■

One in-office test detects RSV fusion protein; results are available in 15 minutes, and the kit has a sensitivity of up to 88% as well as specificity of up to 100%.