

# TOPICS IN Ocular Antiinfectives

## MRSA: An Evolving Enemy

Joseph Blondeau, PhD, FCCP

*Although it has become a familiar nemesis, MRSA continues to evolve a diversity of new strains that can defy empirical treatment based on outdated assumptions.*

The landscape of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) has changed considerably over the last 20 years and continues to evolve in ways that are important to clinicians. Until the early 1990s, for example, most experts as-

sociated MRSA exclusively with health care settings, particularly hospitals and nursing homes.<sup>1</sup> Then, patients from the general community began presenting in emergency rooms with unusually virulent MRSA skin and pulmonary infections. Initially it was thought that these patients must have had some unrecognized exposure to hospital-bred *S. aureus*, but testing soon uncovered bacterial isolates that were genetically distinct from hospital-acquired strains.

Since then, we have seen an explosive spread of MRSA in the general community. In 2008, researchers at Miami's Bascom Palmer Eye Institute reported that between 1994 and 2003, the prevalence of methicillin resistance in *S. aureus* isolates recovered from patient conjunctival swabs jumped from 4.4% to 42.9%.<sup>2</sup> And

last year, cataract surgeons at 10 US sites isolated MRSA or methicillin-resistant *Staphylococcus epidermidis* (MRSE) from the eyelids and conjunctiva of 39% of 399 consecutively seen cataract patients (Table 1).<sup>3</sup> Although nearly a third of the patients in that series had a history of exposure to health care facilities, no such exposure was evident in the vast majority of those colonized with methicillin-resistant isolates (89%). Indeed, analysis confirmed that health care exposure made no statistically significant difference in a person's risk of MRSA carriage (Table 2).

### CA vs HA Evolution

Still, some distinctions remain valid between so-called community-acquired (CA) and hospital-acquired (HA) MRSA strains, and they appear to reflect

TABLE 1

Prevalence of methicillin resistance among *Staphylococcus* (*S. aureus* or *S. epidermidis*) isolated from 399 consecutive cataract patients at 10 study sites.

Clinic Location	Lid Isolates: Total/Resistant (%)	Conjunctival Isolates: Total/Resistant (%)
Louisiana	25/13 (52.0)	15/9 (60.0)
Texas	9/6 (66.7)	9/3 (33.3)
Massachusetts	34/17 (50.0)	19/8 (42.1)
South Carolina	38/16 (42.1)	31/7 (22.6)
Indiana	41/15 (36.6)	25/6 (24)
New York	37/13 (35.1)	21/7 (33.3)
California	25/9 (36.0)	7/2 (28.6)
Florida	45/17 (37.8)	21/9 (42.9)
Utah	35/21 (60.0)	32/16 (50.0)
Pennsylvania	42/15 (35.7)	28/13 (46.4)
TOTAL	331/142 (42.9)	208/80 (38.5)

(Source: Adapted from Reference 3)

### EDITORS

**MARGUERITE B. McDONALD, MD**, is clinical professor of ophthalmology at New York University, New York, and adjunct clinical professor of ophthalmology at Tulane University School of Medicine, New Orleans, Louisiana.

**TERRY KIM, MD**, is a professor of ophthalmology at the Duke University School of Medicine, and the associate director of corneal and refractive surgery services at the Duke Eye Center, likewise in Durham, North Carolina.

**C. STEPHEN FOSTER, MD**, is clinical professor of ophthalmology at Harvard Medical School, a consulting staff member of the Massachusetts Eye and Ear Infirmary, and the founder and president of the Ocular Immunology and Uveitis Foundation and of the Massachusetts Eye Research and Surgery Institution.

*Topics in Ocular Antiinfectives* is published by Candeo Clinical/Science Communications, LLC, and the University of Florida College of Medicine. This publication is administered by an independent editorial board and supported by an unrestricted educational grant from Bausch + Lomb, Inc.

Copyright 2011 Candeo Clinical/Science Communications, LLC. All rights reserved. Neither the University of Florida nor Candeo Clinical/Science Communications, LLC, assume any responsibility for injury or damage to persons or property arising from the use of information or ideas contained in this publication.

### COURSE DIRECTOR

**MARY SMITH, MD**  
University of Florida,  
Gainesville, FL, USA

**UF** Continuing  
Medical Education  
UNIVERSITY OF FLORIDA

evolutionary differences. Methicillin, of course, is not used clinically or even in modern-day susceptibility testing; but “methicillin resistance” remains our shorthand for laboratory-based detection of resistance to all levels of beta-lactam antibiotics, which stop bacterial growth by blocking assembly of key components of the bacterial cell wall.

Like all of today’s MRSA isolates, the earliest strains possessed the *mecA* gene, which encodes a novel penicillin-binding protein. Bacteria that express *mecA* can continue cell division even in the presence of penicillins, cephalosporins, and other beta-lactam antibiotics. The first such isolates were identified in

TABLE 2

Among 399 cataract patients at 10 US sites, only advanced age (>50) and diabetes achieved statistical significance as risk factors for carriage of methicillin-resistant staphylococci on the lids or conjunctiva.

Risk Factor	Odds Ratio (95% CI)	P value
Healthcare worker (HW)*	1.25 (0.61–2.58)	0.54
HW family member	0.73 (0.43–1.26)	0.26
Age (over 50)	1.27 (1.02–1.58)	0.04
Diabetes	0.51 (0.29–0.89)	0.02
Glaucoma	1.44 (0.69–3.00)	0.33

\* employed in a healthcare or long-term nursing care facility (Source: Adapted from Reference 3)

The first such isolates were identified in

the early 1960s, when they sparked a number of hospital outbreaks.<sup>4,5</sup>

## Topics in Ocular Antiinfectives, Issue 18

### STATEMENT OF NEED

Ophthalmologists face numerous challenges in optimizing their competencies and clinical practices in the realm of preventing, diagnosing, and treating ocular infections and their sequelae; these challenges include:

- The widespread “off-label” use of topical ophthalmic antibiotics to prevent and treat serious and sight-threatening infections—given the reality that the most widely used topical antibiotics in ophthalmology have FDA approvals restricted to bacterial conjunctivitis.
- The escalating levels of multi-drug resistance in common ocular pathogens.<sup>1</sup>
- The emergence and increasing prevalence of once-atypical infections that may require diagnostic and treatment techniques relatively unfamiliar to comprehensive ophthalmologists.<sup>2</sup>
- The introduction of new and potentially more efficacious and/or safe ophthalmic antiinfectives.<sup>3</sup>
- The introduction of new and potentially more accurate diagnostic techniques for ophthalmic infections.<sup>4</sup>
- Widespread discussion over the efficacy and safety of novel or alternative delivery techniques and vehicles for prophylactic ophthalmic antibiotics (including but not limited to intracameral injection and topical mucoadhesives).<sup>5,6</sup>
- Increased understanding of the inflammatory damage caused by ocular infections and the best ways to prevent/alleviate inflammation without fueling the growth of pathogenic organisms.

Given the continually evolving challenges described above, *Topics in Ocular Antiinfectives* aims to help ophthalmologists update outdated competencies and narrow gaps between actual and optimal clinical practices. As an ongoing resource, this series will support evidence-based and rational antiinfective choices across a range of ophthalmic clinical situations.

### REFERENCES

1. Asbell PA, Colby KA, Deng S, et al. Ocular TRUST: nationwide antimicrobial susceptibility patterns in ocular isolates. *Am J Ophthalmol*. 2008 Jun;145(6):951–58.
2. Gower EW, Keay LJ, Oechsler RA, et al. Trends in fungal keratitis in the United States, 2001 to 2007. *Ophthalmology*. 2010 Dec;117(12):2263–7.
3. Colin J, Hoh HB, Easty DL, et al. Ganciclovir ophthalmic gel (Virgan 0.15%) in the treatment of herpes simplex keratitis. *Cornea*. 1997;16:393–9.
4. Sambursky R, Tauber S, Schirra F, et al. The RPS adeno detector for diagnosing adenoviral conjunctivitis. *Ophthalmology*. 2006;113(10):1758–64.
5. Akpek EK, Vittitow J, Verhoeven RS, et al. Ocular surface distribution and pharmacokinetics of a novel ophthalmic 1% azithromycin formulation. *J Ocul Pharmacol Ther*. 2009;25:433–9.
6. Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons. Prophylaxis of

postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. *J Cataract Refract Surg*. 2007;33(6):978–88.

**OFF-LABEL USE STATEMENT** This work discusses off-label uses of antiinfective medications.

**GENERAL INFORMATION** This CME program is sponsored by the University of Florida College of Medicine and is supported by an unrestricted educational grant from Bausch + Lomb, Inc.

**Directions:** Select one answer to each question in the exam (questions 1–10) and in the evaluation (questions 11–16). The University of Florida College of Medicine designates this activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. There is no fee to participate in this activity. In order to receive CME credit, participants should read the report, and then take the *posttest*. A score of 80% is required to qualify for CME credit. Estimated time to complete the activity is 60 minutes. On completion, tear out or photocopy the answer sheet and send it to:

University of Florida CME Office  
PO Box 100233  
Gainesville, FL 32610-0233

Or you can take the test online at <http://cme.ufl.edu/ocular>

**DATE OF ORIGINAL RELEASE** April 2011. Approved for a period of 12 months.

**ACCREDITATION STATEMENT** This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Florida College of Medicine and Candeo Clinical/Science Communications, LLC. The University of Florida College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

**CREDIT DESIGNATION STATEMENT** The University of Florida College of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

**TARGET AUDIENCE** This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

### LEARNING OBJECTIVES

Upon completion of this unit the reader will be able to:

1. Revise and update their assessment of patient risk factors for MRSA carriage.
2. List the genetic distinctions between CA-MRSA and HA-MRSA lineages, and apply this knowledge to the effective treatment of ocular infections.
3. Describe the increasing importance of drug susceptibility testing in the treatment of ophthalmic infections, and apply this understanding to clinical practice.
4. Describe the retinal signs of latent *T. gondii* infection, and

state how these signs can be used to assess the patient’s risk from ocular toxoplasmosis.

5. Discuss how patients latently infected with *T. gondii* can be protected against recurrent ocular toxoplasmosis.

### FACULTY AND DISCLOSURE STATEMENTS

**Marguerite B. McDonald, MD, FACS**, is a clinical professor of ophthalmology at New York University, New York, NY, and an adjunct clinical professor of ophthalmology at Tulane University School of Medicine, New Orleans, LA. She states that in the previous twelve months she has been a consultant for Abbott Medical Optics, Allergan, Bausch + Lomb, Inspire Pharmaceuticals, Santen Pharmaceutical, Vistakon, Essilor, Focus Laboratories, and Pfizer.

**C. Stephen Foster, MD, FACS, FFAO, FACR**, is clinical professor of ophthalmology at Harvard Medical School, a consulting staff member of the Massachusetts Eye and Ear Infirmary, and the founder and president of the Ocular Immunology and Uveitis Foundation and of the Massachusetts Eye Research and Surgery Institution. He states that in the past twelve months he has been a consultant to Abbott Medical Optics, ISTA Pharmaceuticals, Lux Biosciences, and Novartis Pharmaceuticals; he has been on the speakers bureau of AMO, Allergan, Bausch + Lomb, Inspire, ISTA, and Lux Biosciences; and he has received grant support from AMO, Allergan, Eyegate Pharma, Lux Biosciences, and Novartis. He is also an equity owner of Eyegate Pharma.

**Terry Kim, MD**, is a professor of ophthalmology at the Duke University School of Medicine, and the associate director of corneal and refractive surgery services at the Duke Eye Center, likewise in Durham, NC. He states that in the past twelve months he has been a consultant to Alcon, Allergan, Inspire, ISTA, OSI, Ocular Therapeutics, Pfizer, and PowerVision.

**Joseph Blondeau, PhD, FCCP**, is an adjunct professor of microbiology and immunology and a clinical associate professor of pathology and ophthalmology at the University of Saskatchewan and heads the department of clinical microbiology at the Royal University Hospital and the Saskatoon Health Region, all in Saskatoon, Saskatchewan, Canada. He says that in the previous twelve months he has received research grants from Allergan and has been a consultant for Allergan and Bausch + Lomb.

**Rubens Belfort Jr., MD, PhD**, is a professor in the department of ophthalmology at the Federal University of São Paulo and the Hospital São Paulo, Brazil. He states that in the past twelve months he has not had a financial relationship with any commercial organization that produces, markets, re-sells, or distributes healthcare goods or services consumed by, or used on, patients.

**DISCLAIMER** Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and professional development. The information presented in this activity is not meant to serve as a guideline for patient care. Procedures, medications, and other courses of diagnosis and treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients’ conditions and possible contraindications or dangers in use, applicable manufacturer’s product information, and comparison with recommendations of other authorities.

**COMMERCIAL SUPPORTERS** This activity is supported by an educational grant from Bausch + Lomb, Inc.

## CORE CONCEPTS

- MRSA has evolved into a multitude of genetically distinct strains that vary widely in drug resistance, transmissibility, and virulence.
- Non-healthcare workers are now just as likely as healthcare workers to carry MRSA on the conjunctiva and lid margins.
- While CA-MRSA strains tend to be less multidrug-resistant, some are associated with unusually invasive infections of the eye and orbit.
- Only specimen collection and drug-sensitivity testing can reliably guide the antimicrobial treatment of MRSA infections.
- The addition of BAK enhances the anti-MRSA efficacy of topical fluoroquinolones.
- The addition of BAK decreases a fluoroquinolone's propensity to select for drug-resistant strains of staphylococci.
- The increasing prevalence of MRSA heightens the need for scrupulous hygiene and sanitation in clinical practice.

From those early isolates, a multitude of successful clones survived and even thrived in hospital environments, where heavy use of antimicrobials continued to select for their carriage on the skin and mucosa of patients. As hospitals switched to other antibiotics to fight staphylococcal infections, hospital MRSA lineages picked up additional resistance genes, which came to surround the *mecA* gene within the staphylococcal chromosomal cassette (SCC), a mobile genetic element that spreads freely between staphylococcal species. As a result, hospital-acquired strains tend to be multidrug-resistant to clindamycin, ciprofloxacin, gentamicin and trimethoprim/sulfa antibiotics. Today, some of the most extensively drug-resistant staphylococcal isolates also demonstrate reduced sensitivity to vancomycin.<sup>6</sup>

## The Rise of CA-MRSA

As noted, the first CA-MRSA infections were assumed to have been caused by microbial “escapees” from hospitals and nursing homes. However, genetic analysis showed that the CA strains lacked the more extensive SCC-mec elements that gave hospital strains their broader multidrug resistance.<sup>7</sup> Further distinguishing the most dangerous of the CA strains was the presence of the Panton-Valentine leukocidin (PVL) gene, a virulence marker associated with bacteremia and necrotizing skin and pulmonary infections.<sup>8,9</sup>

What explains the continued spread of CA-MRSA strains? Their growing predominance appears to be based less on drug resistance or virulence than on their enhanced fitness—particularly their ability to spread readily between contacts and persistently colonize the skin and mucosa of new hosts.<sup>10,11</sup>

In North America, for example, the USA300 and USA400 CA-MRSA clones tend to displace less tenacious *S. aureus* strains soon after they move into a new community.<sup>12</sup> These MRSA strains spread particularly rapidly under conditions of increased physical contact and reduced hygiene—for example among prison inmates, team athletes, military personnel, and young children in daycare centers. In 2007, a commentary in the *Canadian Medical Association Journal* described the “5 C’s” of CA-MRSA (Table 3).<sup>13</sup>

TABLE 3

The 5 C’s of heightened CA-MRSA transmission.

Crowding
Frequent skin contact
Compromised skin
Sharing of contaminated personal care items
Compromised cleanliness

(Source: Adapted from Reference 13)

MRSA’s growing predominance among healthy community members also challenges long-held assumptions about the reduced ability of drug-resistant strains to compete in the absence of antibiotic use as a selective pressure. We now know that many types of bac-

teria can harbor resistance genes with negligible effect on their overall fitness.<sup>14</sup>

What this means going forward is that, with more and more people colonized with MRSA, the reservoir for dissemination to others continues to grow, as does the risk of opportunistic MRSA infections. This is of particular concern in ophthalmology because the vast majority of postoperative endophthalmitis isolates trace to a patient’s own resident microflora.<sup>15</sup>

## CA vs HA: Clinical Guidance

Given the growing predominance of CA-MRSA in our communities, we can no longer make blanket assumptions about a patient’s risk of MRSA carriage based on their history of exposure to health care settings. For that matter, it bears mentioning that methicillin resistance is even more common among prevalent strains of *S. epidermidis*, which can likewise cause sight-threatening infections.<sup>16</sup>

Meanwhile, HA-MRSA isolates are continually entering the community with health care workers and discharged hospital patients, just as CA-MRSA isolates continue to enter health care settings on workers and newly admitted patients. To date, we do not have evidence of extensive transfer of genetic resistances between “hospital” and “community” MRSA lineages. However, we know that staphylococci carry their resistance genes on mobile genetic elements, so horizontal transfer is possible.

## Culture and Susceptibility Testing

All these factors bolster the argument that the only reliable way to select an effective antibiotic for a given infection is through culture and drug-susceptibility testing. Unfortunately, many ophthalmologists do not send specimens for culture and susceptibility testing except when confronted with treatment failure.

Some ophthalmologists object that the breakpoints used in laboratory susceptibility testing are based on “reasonably achievable” systemic drug concentrations and offer poor guidance for the topical application of ophthalmic drugs, which can achieve significantly higher local concentrations. I would argue the oppo-

site—that laboratory results can provide practical guidance as to when it might be advantageous to increase the frequency of topical application to overcome such dose-dependent resistance. This may prove particularly relevant with current generation fluoroquinolones, resistance to which generally involves elevated minimum inhibitory concentration (MIC) values, rather than absolute resistance.<sup>17</sup>

It would likewise seem reasonable to take advantage of such guidance when using ophthalmic antibiotics for perioperative prophylaxis—in this case based on a preoperative culture of the patient’s conjunctiva and lid margins.

### Selecting an Agent for Treatment or Prophylaxis

Studies demonstrate that ophthalmic formulations of current-generation fluoroquinolones differ in their efficacy against MRSA eye infections. Our research shows, for example, that combining a current generation fluoroquinolone with the preservative benzalkonium chloride (BAK) achieves an antimicrobial synergy that is particularly effective against MRSA.<sup>18</sup> In addition to lowering fluoroquinolone MIC values for MRSA, the addition of BAK also reduces the effective mutant prevention concentration (MPC), thereby decreasing a drug’s propensity to select for fluoroquinolone-resistant strains of staphylococci.<sup>19</sup> At present, two fourth-generation fluoroquinolones—besifloxacin and gatifloxacin—have BAK-preserved ophthalmic formulations.

Our findings are backed up by studies showing that, compared to moxifloxacin and ciprofloxacin, besifloxacin demonstrates overall superior bactericidal potency and speed of action against both fluoroquinolone-susceptible and fluoroquinolone-resistant isolates of *S. aureus* and *S. epidermidis*.<sup>20,21</sup>

### Beware of Virulence

A laboratory susceptibility profile suggestive of CA-MRSA should heighten the clinician’s vigilance for the kind of invasively aggressive infections associated with the PVL virulence marker. The USA300 clone, in particular, has been linked to unusually damaging and rapidly

progressing infections of the eye and orbit (Figure 1).<sup>22</sup> The potential for such virulence also underscores the importance of optimizing anti-infective therapy with laboratory culture and susceptibility results as soon as possible—whatever the clinician’s initial suspicions may be.



**FIGURE 1** Community-acquired MRSA isolates expressing Panton-Valentine leukocidin (PVL) have been associated with unusually virulent and invasive infections of the eye and orbit.

Finally, CA-MRSA’s double threat of virulence and drug resistance should serve as a wake-up call for increased vigilance in physician/staff hygiene and office/surgical suite sanitation. The advice may sound dated, but as a microbiologist, I can assure you that there is nothing as important as frequently and effectively washing your hands.

*Joseph Blondeau, PhD, FCCP, is an adjunct professor of microbiology and immunology and a clinical associate professor of pathology and ophthalmology at the University of Saskatchewan and heads the department of clinical microbiology at the Royal University Hospital and the Saskatoon Health Region, all in Saskatoon, Saskatchewan, Canada.*

### REFERENCES

- O’Toole RD, Drew WL, Dahlgren BJ, Beaty HN. An outbreak of methicillin-resistant *Staphylococcus aureus* infection. Observations in hospital and nursing home. *JAMA*. 1970 Jul 13;213(2):257-63.
- Cavuto K, Zutshi D, Karp CL, Miller D, Feuer W. Update on bacterial conjunctivitis in South Florida. *Ophthalmology*. 2008 Jan;115(1):51-6.
- Olson R, Donnenfeld E, Bucci FA, et al. Methicillin resistance of *Staphylococcus* species among health care and nonhealth care workers undergoing cataract surgery. *Clin Ophthalmol*. 2010 Dec 10;4:1505-14.
- Barber M. Methicillin-resistant staphylococci. *J Clin Pathol*. 1961;14:385-393.
- Jevons MP, Coe AW, Parker MT. Methicillin resistance in staphylococci. *Lancet*. 1963;1(7287):904-907.
- Howe RA, Monk A, Wootton M, Walsh TR, Enright MC. Vancomycin susceptibility within methicillin-resistant *Staphylococcus aureus* lineages. *Emerg Infect Dis*. 2004 May;10(5):855-7.
- Centers for Disease Control and Prevention (CDC). Four pediatric deaths from community-

- acquired methicillin-resistant *Staphylococcus aureus* — Minnesota and North Dakota, 1997-1999. *MMWR Morb Mortal Wkly Rep*. 1999 Aug 20;48(32):707-10.
- Diep BA, Sensabaugh GF, Somboonna N, Carleton HA, Perdreau-Remington F. Widespread skin and soft-tissue infections due to two methicillin-resistant *Staphylococcus aureus* strains harboring the genes for Panton-Valentine leukocidin. *J Clin Microbiol*. 2004 May;42(5):2080-4.
- Blaine KP, Tuohy MJ, Wilson D, et al. Progression to bacteremia in critical care patients colonized with methicillin-resistant *Staphylococcus aureus* expressing Panton-Valentine leukocidin. *Diagn Microbiol Infect Dis*. 2010 Sep;68(1):28-33.
- Yamamoto T, Nishiyama A, Takano T, et al. Community-acquired methicillin-resistant *Staphylococcus aureus*: community transmission, pathogenesis, and drug resistance. *J Infect Chemother*. 2010 Aug;16(4):225-54.
- Barbier F, Lebeaux D, Hernandez D, et al. High prevalence of the arginine catabolic mobile element in carriage isolates of methicillin-resistant *Staphylococcus epidermidis*. *J Antimicrob Chemother*. 2011 Jan;66(1):29-36.
- Shukla SK, Karow ME, Brady JM, et al. Virulence genes and genotypic associations in nasal carriage, community-associated methicillin-susceptible and methicillin-resistant USA400 *Staphylococcus aureus* isolates. *J Clin Microbiol*. 2010 Oct;48(10):3582-92.
- Hawkes M, Barton M, Conly J, Nicolle L, Barry C, Ford-Jones EL. Community-associated MRSA: superbug at our doorstep. *CMAJ*. 2007 Jan 2;176(1):54-6.
- Levin BR, Cornejo OE. The population and evolutionary dynamics of homologous gene recombination in bacterial populations. *PLoS Genet*. Epub 2009 Aug 14.
- Speaker MG, Milch FA, Shah MK, Eisner W, Kreiswirth BN. Role of external bacterial flora in the pathogenesis of acute postoperative endophthalmitis. *Ophthalmology*. 1991 May;98(5):639-49.
- Barbier F, Ruppé E, Hernandez D, et al. Methicillin-resistant coagulase-negative staphylococci in the community: high homology of SCCmec IVa between *Staphylococcus epidermidis* and major clones of methicillin-resistant *Staphylococcus aureus*. *J Infect Dis*. 2010 Jul 15;202(2):270-81.
- Proksch JW, Ward KW. Ocular pharmacokinetics/pharmacodynamics of besifloxacin, moxifloxacin, and gatifloxacin following topical administration to pigmented rabbits. *J Ocul Pharmacol Ther*. 2010 Oct;26(5):449-58.
- Blondeau JM, Borsos S, Hesje CK. Antimicrobial efficacy of gatifloxacin and moxifloxacin with and without benzalkonium chloride compared with ciprofloxacin and levofloxacin against methicillin-resistant *Staphylococcus aureus*. *J Chemother*. 2007 Apr;19(2):146-51.
- Hesje CK, Borsos SD, Blondeau JM. Benzalkonium chloride enhances antibacterial activity of gatifloxacin and reduces its propensity to select for fluoroquinolone-resistant strains. *J Ocul Pharmacol Ther*. 2009 Aug;25(4):329-34.
- Haas W, Pillar CM, Hesje CK, Sanfilippo CM, Morris TW. Bactericidal activity of besifloxacin against staphylococci, *Streptococcus pneumoniae* and *Haemophilus influenzae*. *J Antimicrob Chemother*. 2010 Jul;65(7):1441-7.
- Haas W, Pillar CM, Zurenko GE, Lee JC, Brunner LS, Morris TW. Besifloxacin, a novel fluoroquinolone, has broad-spectrum in vitro activity against aerobic and anaerobic bacteria. *Antimicrob Agents Chemother*. 2009 Aug;53(8):3552-60.
- Rutar T, Chambers HF, Crawford JB, et al. Ophthalmic manifestations of infections caused by the USA300 clone of community-associated methicillin-resistant *Staphylococcus aureus*. *Ophthalmology*. 2006 Aug;113(8):1455-62.

# Ocular Toxoplasmosis: Advances in Understanding and Treatment

RUBENS BELFORT JR, MD, PHD

*Latent Toxoplasma gondii infection affects up to one-third of the world's population; and in both the US and worldwide, ocular toxoplasmosis is the most common cause of posterior uveitis, as well as infectious uveitis in non-HIV infected patients. Advances in disease understanding and clinical experience are improving diagnosis and treatment, though large-scale clinical trials are badly needed to define the most effective management strategies.*

*Toxoplasma gondii*, an intracellular protozoan parasite, is the leading cause of posterior uveitis. Although acute ocular toxoplasmosis can be treated with systemic antimicrobials and steroids, treatment does not prevent sight-threatening recurrences, which likely result from the reactivation of antibiotic-resistant cysts in the retina or related inflammatory mechanisms. With a dearth of clinical research on the subject, those of us who regularly see and treat ocular toxoplasmosis must rely instead on decades of experience to guide both short-term and long-term management.

## A Common Parasite

Antibody evidence of prior *T. gondii* infection can be found in up to one-third of the world population. In the US, antibody studies suggest that prevalence has declined considerably in recent decades to around 11%, with higher rates among those over age 30 and lower rates among children.<sup>1</sup> These rates vary between regions, with prevalence highest in the southern states, where dietary habits and socioeconomic status may predispose to exposure and infection.<sup>1</sup>

We have no reliable data on the percentage of latently infected persons who develop ocular toxoplasmosis. Nor do we understand what triggers this reactivation in immunocompetent individuals. We do know that the tendency for ocular involvement varies between *T. gondii*'s clonal lineages. Many of the strains seen in Brazil, for example, stand out for their ocular virulence. In Southern Brazil, a quarter to a third of the population has toxoplasmic retinal scars.<sup>2</sup> In North America, where less-virulent strains predominate, ocular

toxoplasmosis is believed to occur in around 2% of seropositive individuals.<sup>3</sup>

## Primary Infection and Latency

The infectious lifecycle of *T. gondii* is well described. Human infection occurs by ingestion of cysts or congenital transmission from a newly infected mother. Viable cysts can be found in raw or undercooked meat (particularly pork or chicken), unfiltered water (chlorination alone is insufficient to eradicate cysts), and the feces of cats that spend extended periods outdoors. In addition, outbreaks have been traced to the probable inhalation of aerosolized cysts, which can occur in dusty environments such as stables.<sup>3</sup>

Once ingested, the cysts open in the small intestine, allowing the body-wide dissemination of rapidly dividing tachyzoites. The active parasite can invade virtually all cell types but has a particular affinity for the tissues of the nervous system, including the retina. This may be due to the relatively immune-privileged status of these tissues.

Most physicians advise pregnant women to avoid cleaning the litter boxes of outdoor cats, given the potentially devastating consequences of congenital infection. (Handling cats—as opposed to their feces—is not thought to create an infection risk.<sup>4</sup>) During primary infection, tachyzoites can pass through the placenta, and congenital infection can result in miscarriage, stillbirth, or birth defects, particularly when infection occurs in the first trimester.<sup>5</sup> At birth, congenitally infected infants may have bilateral ocular toxoplasmosis with significant macular involvement.

## CORE CONCEPTS

- *T. gondii* establishes lifelong latent infection, with tissue cysts commonly found in many parts of the body including the retina.
- An estimated 11% of the US population is latently infected with *T. gondii*, with higher prevalence in southern states.
- In the US, around 2% of seropositive individuals develop ocular toxoplasmosis.
- Primary ocular toxoplasmosis is seldom sight-threatening, but the risk of severe retinal necrosis and vision loss increases with each recurrence.
- Treatment with systemic antimicrobials can usually control acute ocular toxoplasmosis. Systemic steroids may help control the associated inflammation.
- Steroids should be used only in conjunction with antimicrobials.

Fortunately, most congenitally infected infants are born without signs or symptoms of disease.<sup>6</sup> Until the 1990s it was widely believed that almost all cases of ocular toxoplasmosis resulted from congenital infection. We now know that the opposite is true: Most cases are the result of reactivation of infections acquired after birth. Post-natal primary infections likewise tend to be asymptomatic.

## Reactivation

Commonly, initial infection with *T. gondii* is followed by a latency period that lasts for months, years, or even decades. Children infected as toddlers, for example, often develop symptomatic ocular toxoplasmosis between ages 11 and 15.

Compared to primary infection, reactivation of retinal cysts is far more sight-threatening, with the threat increasing with each recurrence, as well as with advancing age.<sup>7</sup> As mentioned,

reactivation triggers are little understood in the immunocompetent population. However both systemic steroids and subconjunctival steroid injections are associated with ocular *T. gondii* reactivation, although this can be prevented by co-administration of appropriate antimicrobials.<sup>8</sup> Immunosuppressive cancer drugs and uncontrolled AIDS are likewise associated with particularly severe forms of recurrent disease, including extensive retinal necrosis.

## Diagnosis

Often, routine ophthalmic examination reveals toxoplasmic lesions on an otherwise healthy retina (Figure 1). These pigmented scars do *not* represent active disease; rather, they are the tell-tale signs of prior ocular toxoplasmosis. The patient may be at risk of developing other ocular lesions.

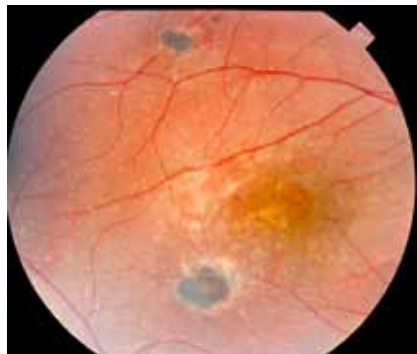
As a rule, patients with symptomatic ocular toxoplasmosis first seek medical care for decreased visual acuity. Such symptoms tend to be unilateral and include hazy or blurred vision, frequently accompanied by floaters or more significant dark spots in the field of vision. Inflammatory cells are often present in the anterior chamber. Iridocyclitis and red eye may likewise be evident, and a benign and self-limited elevation in intraocular pressure occurs in approximately 10% to 20% of patients.<sup>9</sup> Some acute symptoms tend to be fleeting and may have resolved by the time of examination. So it is important to inquire about them on history taking.

The hallmark of ocular toxoplasmosis is a necrotizing focal retinochoroiditis with vitritis; and if this appears satellite to an old scar, the clinical picture is pathognomonic. Secondary vasculitis is commonly present and, depending on the severity of the vasculitis, retinal hemorrhage may likewise be evident (Figure 2). Unfortunately, the extensive vitreal opacities that also characterize the condition can interfere with direct viewing of retinal lesions.

Other vitreoretinal complications can include retinal detachment, vitreous hemorrhage, epiretinal membranes, and

areas of choroidal neovascularization. Long-term complications can include cataracts and cystoid macular edema.

In severely immunocompromised



**FIGURE 1** These pigmented toxoplasmic lesions do *not* represent active disease, but signal prior infection and presumed latency. Image courtesy of Rubens Belfort, MD.



**FIGURE 2** The active lesions appear as grey-white foci of retinal necrosis with adjacent retinochoroiditis, vasculitis, hemorrhage, and/or vitritis. Image courtesy of Rubens Belfort, MD.

individuals, differential diagnosis should include ocular herpes (simplex or zoster) and cytomegalovirus, which can present concurrently.

Serological testing can aid diagnosis and includes either enzyme-linked immunosorbent assay (ELISA) or immunofluorescent antibody (IFA) evidence of both IgM and IgG antibodies directed at *T. gondii*. IgG antibodies alone simply indicate past infection, and their absence is strong evidence against ocular toxoplasmosis. By contrast, IgM antibodies tend to spike during acute infection.<sup>10</sup> In some cases, polymerase chain reaction (PCR) can be used to identify toxoplasmic antigens in the aqueous or vitreous.

## Treatment

Without large clinical studies for guidance, we have no definitive evidence of the superiority of any one treatment regimen. In 2002, a survey by the American Uveitis Society found members using 24 different protocols and nine different antiparasitic drugs.<sup>11</sup> As a result, I describe our treatment guidelines as more “eminence based” than “evidence based.” They represent the collective clinical experience of the world’s leading authorities.

That said, all treatment regimens rely primarily on systemic antimicrobial drugs, with or without systemic steroids for the control of extensive inflammation. The most commonly used antimicrobials include pyrimethamine, sulfadiazine, clindamycin, and trimethoprim-sulfamethoxazol.<sup>12</sup>

My preferred treatment consists of pyrimethamine and sulfadiazine with a systemic steroid, and most retinal specialists now accept this “triple therapy” as the standard regimen for ocular toxoplasmosis.

Pyrimethamine inhibits folic acid metabolism and, so, warrants the addition of folinic acid supplementation. In addition, pyrimethamine is generally contraindicated for treatment of pregnant women owing to possible teratogenic effects. In some countries, spiramycin is used as the alternative during pregnancy, and we have some evidence that it reduces the risk of *T. gondii* transmission to the fetus.<sup>13</sup>

We lack the clinical studies needed to determine with certainty whether steroids are of benefit to our patients. When considering the addition of steroid therapy to quell sight-threatening inflammation, factors to weigh include the proximity of active lesions to the macula and optic disc, the number and size of lesions, and the severity and duration of the vitreous inflammation. In other words, the degree of threat should guide the decision.

On one thing all experts agree: Steroids should *never* be used in these patients without antimicrobials, as the resulting immunosuppression can

## CLINICAL MANAGEMENT OF OCULAR TOXOPLASMOSIS

There is insufficient clinical trial data to demonstrate the superiority of any one treatment regimen. The author recommends the following:

- Treatment of active disease
  - Pyrimethamine, sulfadiazine, and steroid
- Prophylaxis for those with continued recurrences: Trimethoprim (160 mg)/sulfamethoxazole (800 mg) every 3 days

increase the severity of active disease or trigger reactivation of latent disease.

In general, short-term treatment with antimicrobials and steroids achieves prompt resolution of acute ocular toxoplasmosis. In rare cases, systemic treatment is ineffective or contraindicated. For these rare patients, we have used intravitreal injections of clindamycin and steroid with good results.<sup>14</sup> However, the risks associated with these invasive procedures should make their use a last resort.

### Prophylaxis

Treatment of acute ocular toxoplasmosis does not protect against the recurrences that pose the greatest threat to vision. In patients with frequent recurrences or high risk of vision loss, we look to long-term prophylaxis to preserve sight. We consider trimethoprim-sulfamethoxazole a good choice for long-term prophylaxis, as there are safety concerns when either pyrimethamine or sulfadiazine is used on a chronic basis.

In 2002, we published the results of a small clinical trial, randomizing 124 patients with a history of recurrent ocular toxoplasmosis to either one tablet of trimethoprim (160 mg)/sulfamethoxazole (800 mg) every 3 days, or observation without treatment. Over 20 consecutive months, recurrence developed in four (6.6%) of the treated patients vs 15 (23%) of the controls.<sup>15</sup> Since then we and many others have kept patients on this prophylactic regimen for 7 years or more—significantly reducing recurrence

rates with no evidence of complications.

From our understanding of *T. gondii*'s life cycle, we believe that the cysts themselves are protected from antimicrobial drugs. Rather, keeping antimicrobials in circulation may aid the rapid killing of emerging tachyzoites. This theory is backed by the prophylactic regimen's ability to prevent central nervous system toxoplasmosis in AIDS patients, as well as our observation that stopping prophylactic treatment for ocular toxoplasmosis, even after years, results in a return to the baseline rate of recurrence.

### Pars Plana Vitrectomy and Cataract Removal

As noted, recurrent ocular toxoplasmosis predisposes to retinal detachment, as well as to vitreal opacification and cataracts, which compromise both the patient's sight and the ophthalmologist's ability to view the retina. The clinician's need to view the retina is particularly crucial in cases of nonverbal children with cicatricial toxoplasmosis. As a result, pars plana vitrectomy may be indicated when cataract and vitreous opacities are present. Usually the removal of the opacities is performed concurrently with lens removal and IOL insertion. Surgery should take place during a disease- and inflammation-free period. As vitreous opacification often resolves on its own, pars plana vitrectomy in the absence of cataract or retinal detachment should be delayed for at least 6 months, with close patient observation.

### Future Progress

Even one large clinical trial could provide us with the guidance needed to definitively establish the superiority of one or more of the many treatment regimens now in use. Meanwhile, there has been progress in the development of diagnostic tests that can make strain-specific *T. gondii* identifications and help us to predict the degree of virulence that we can expect with a given case.

Above all, perhaps, we need an effective vaccine. While there is research being directed toward this goal, there are no vaccines for human use on the near

horizon. Even those being developed for livestock are associated with unacceptable side effects including birth defects.

*Rubens Belfort Jr, MD, PhD, is a professor in the department of ophthalmology at the Federal University of São Paulo and the Hospital São Paulo, Brazil.*

### REFERENCES

1. Jones JL, Kruszon-Moran D, Sanders-Lewis K, Wilson M. *Toxoplasma gondii* infection in the United States, 1999–2004, decline from the prior decade. *Am J Trop Med Hyg*. 2007 Sep;77(3):405–10.
2. Glasner PD, Silveira C, Kruszon-Moran D, et al. An unusually high prevalence of ocular toxoplasmosis in Southern Brazil. *Am J Ophthalmol*. 1992;114:136–44.
3. Holland GN. Ocular toxoplasmosis: a global reassessment. Part I: epidemiology and course of disease. *Am J Ophthalmol*. 2003; 136:973–88.
4. Elmore SA, Jones JL, Conrad PA. *Toxoplasma gondii*: epidemiology, feline clinical aspects, and prevention. *Trends Parasitol*. 2010 Apr;26(4):190–6.
5. Feldman DM, Timms D, Borgida AF. Toxoplasmosis, parvovirus, and cytomegalovirus in pregnancy. *Clin Lab Med*. 2010 Sep;30(3):709–20.
6. Wallon M, Kodjikian L, Binquet C. Long-term ocular prognosis in 327 children with congenital toxoplasmosis. *Pediatrics*. 2004 Jun;113(6):1567–72.
7. Holland GN. Ocular toxoplasmosis: the influence of patient age. *Mem Inst Oswaldo Cruz*. 2009;104(2):351–57.
8. de-la-Torre A, Rios-Cadavid AC, Cardozo-García CM, Gomez-Marin JE. Frequency and factors associated with recurrences of ocular toxoplasmosis in a referral centre in Colombia. *Br J Ophthalmol*. 2009 Aug;93(8):1001–4.
9. Hovakimyan A, Cunningham ET Jr. Ocular toxoplasmosis. *Ophthalmol Clin N Am*. 2002;15:327–33.
10. Commodaro AG, Belfort RN, Rizzo LV, et al. Ocular toxoplasmosis—an update and review of the literature. *Mem Inst Oswaldo Cruz*. 2009;104(2):345–50.
11. Holland GN, Lewis KG. An update on current practices in the management of ocular toxoplasmosis. *Am J Ophthalmol*. 2002;134:103–14.
12. Antoniazzi E, Guagliano R, Meroni V, Pezzotta S, Bianchi PE. Ocular impairment of toxoplasmosis. *Parassitologia*. 2008 Jun;50(1–2):35–6.
13. Cortina-Borja M, Tan HK, Wallon M, et al. Prenatal treatment for serious neurological sequelae of congenital toxoplasmosis: an observational prospective cohort study. *PLoS Med*. 2010 Oct 12;7(10). pii: e1000351.
14. Lowder C, Belfort R Jr, Lightman S, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol*. 2011 Jan 10. [Epub ahead of print]
15. Silveira C, Belfort R Jr, McCool C, et al. The effect of long-term intermittent trimethoprim/sulfamethoxazole treatment on recurrences of toxoplasmic retinochoroiditis. *Am J Ophthalmol*. 2002 Jul;134(1):41–6.

### UPCOMING TOPICS

- Beyond MRSA: Emerging Bacterial Pathogens
- Closing the Gaps in Surgical and Procedural Sanitation

## EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 18

This CME program is sponsored by the University of Florida College of Medicine and supported by an unrestricted educational grant from Bausch + Lomb, Inc. **DIRECTIONS:** Select the one best answer to each question in the Exam (Questions 1-10) and in the Evaluation (Questions 11-16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this activity for a maximum of 1.0 AMA PRA Category 1 Credit™. There is no fee to participate in this activity. You can take the test online at <http://cme.ufl.edu/ocular>.

- In a recent study, methicillin-resistant staphylococcus was isolated from the eyelids and conjunctiva of \_\_\_\_% of 399 cataract patients seen consecutively at 10 sites across the United States.
  - 9%
  - 39%
  - 69%
  - 89%
- In the above study, which of the following factors was/were associated with a significantly increased risk of methicillin-resistant ocular isolates?
  - Age over 50 years
  - Being a healthcare worker
  - Being a relative of a healthcare worker
  - All of the above are correct
- Which of the following appears to be an intrinsic factor in the continued spread of the most successful CA-MRSA strains?
  - Extensive drug resistance
  - Extreme virulence
  - Enhanced ability to spread between contacts
  - Lowered susceptibility to povidone-iodine
- Which of the following factors is known to promote the transmission of CA-MRSA?
  - Overuse of antibiotics and hand sanitizers
  - Hot and humid climate
  - Cold and dry climate
  - Crowding and broken skin
- Ocular toxoplasmosis is thought to occur in what percentage of latently infected North Americans?
  - 0.02%
  - 2%
  - 22%
  - More than 50%
- How does the addition of benzalkonium chloride (BAK) decrease a drug's propensity to select for resistant organisms?
  - By sterilizing the ocular surface
  - By reducing an antibiotic's mutant prevention concentration
  - Both A and B
  - Neither A nor B
- Which of the following is/are known to trigger recurrence of ocular toxoplasmosis in immunocompetent persons?
  - Systemic steroid treatment
  - Subconjunctival steroid
  - Both A and B are correct
  - Neither A nor B is correct
- The prevalence of latent *T. gondii* infection in the US is estimated to be:
  - 0.01%
  - 1%
  - 11%
  - 41%
- Which of the following is a common sign of latent ocular toxoplasmosis?
  - Extensive retinal necrosis
  - Vitreous infiltrates
  - Floater that obscures vision
  - Small, pigmented retinal lesions
- Which of the following is/are appropriate for long-term suppression of recurrent ocular toxoplasmosis?
  - Pyrimethamine/sulfadiazine
  - Trimethoprim/sulfamethoxazole
  - Topical ophthalmic fluoroquinolones
  - Ketoconazole

## EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 18

This CME program is sponsored by the University of Florida and Candeo Clinical/Science Communications, LLC, and supported by an unrestricted educational grant from Bausch + Lomb, Inc. Mail to: University of Florida CME Office, PO Box 100233, Gainesville, FL 32610-0233. **DIRECTIONS:** Select the one best answer for each question in the exam above (Questions 1–10). Participants must score at least 80% on the questions and complete the entire Evaluation (Questions 11–16) to receive CME credit.

### ANSWERS:

- |            |             |
|------------|-------------|
| 1. A B C D | 6. A B C D  |
| 2. A B C D | 7. A B C D  |
| 3. A B C D | 8. A B C D  |
| 4. A B C D | 9. A B C D  |
| 5. A B C D | 10. A B C D |

### EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

- Extent to which the activity met the identified
  - Objective 1: 1 2 3 4 5
  - Objective 2: 1 2 3 4 5
  - Objective 3: 1 2 3 4 5
  - Objective 4: 1 2 3 4 5
  - Objective 5: 1 2 3 4 5
- Rate the overall effectiveness of how the activity:
  - Related to my practice: 1 2 3 4 5
  - Will influence how I practice: 1 2 3 4 5
  - Will help me improve patient care: 1 2 3 4 5
  - Stimulated my intellectual curiosity: 1 2 3 4 5
  - Overall quality of material: 1 2 3 4 5
  - Overall met my expectations: 1 2 3 4 5
  - Avoided commercial bias/influence: 1 2 3 4 5
- Will the information presented cause you to make any changes in your practice? Yes No
- If yes, please describe: \_\_\_\_\_
- How committed are you to making these changes?
  - 1 2 3 4 5
- Are future activities on this topic important to you?
  - Yes No

If you wish to receive credit for this activity, please fill in the following information. Retain a copy for your records —

### PLEASE PRINT CLEARLY

FIRST NAME LAST NAME DEGREE

ORGANIZATION/INSTITUTE

ADDRESS LINE 1

ADDRESS LINE 2

CITY STATE ZIP

PHONE FAX

E-MAIL ADDRESS