Current knowledge about and recommendations for ocular methicillin-resistant *Staphylococcus aureus*

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*Staphylococcus aureus* is the most important and common pathogen that infects patients following cataract surgery, laser in situ keratomileusis, and photorefractive keratectomy. It is reported to be the second most common pathogen causing bacterial keratitis around the world. Of special concern are increasing reports of postoperative methicillin-resistant *S aureus* (MRSA) infection. For example, MRSA wound infections have been reported with clear corneal phacoemulsification wounds, penetrating keratoplasty, lamellar keratoplasty, and following ex vivo epithelial transplantation associated with amniotic membrane grafts. These and other data suggest that MRSA has become increasingly prevalent worldwide. In this article, we review the current medical literature and describe the current challenge of ocular MRSA infections. Recommendations are made based on an evidence-based review to identify, treat, and possibly reduce the overall problem of this organism.

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Since the first scientific observation of what would now be called an antibiotic effect was made in the 19th century by French chemist Louis Pasteur, a struggle against bacterial mutations and adaptation has been waging. Ophthalmology has played a role in this battle beginning with Carl Crede's pioneering work in the 1800s to battle ophthalmia neonatorum with silver nitrate. Over time, the ever-mutating bacteria have seemed to be a step ahead, able to select several sentinel colonies that would go unnoticed under a normal wild-type scenario but when under attack with antibiotics become important. These protective resistance mutations enable the pathogens to survive and thrive in an otherwise hostile environment. The latest and, to date, the toughest combatant in the infectious disease arms race is methicillin-resistant *Staphylococcus aureus* (MRSA). This article reviews the current medical literature, describes the current problem, and makes recommendations based on an evidence-based review.

*Staphylococcus aureus*, literally the “golden cluster seed” or “the seed gold,” was discovered in Aberdeen, Scotland, in 1880 by the surgeon Sir Alexander Ogston from pus in surgical abscesses. *Staphylococcus aureus* is frequently found in the nose and skin of a person. About 20% of the population are long-term carriers of *S aureus*. The bacterium is one of the most common causes of nosocomial infections, often causing postsurgical wound infections, such as after cataract surgery. Each year approximately 500,000 patients in American hospitals contract a *Staphylococcal* species infection.
**DEVELOPMENT OF RESISTANCE**

Penicillins were the first large class of antibiotics that were effective against a wide range of bacteria, including *S. aureus*. However, due to bacterial mutation, resistance to this class of antibiotic made it ineffective against β-lactamase-producing organisms, including many gram-positives such as *S. aureus*. The β-lactamase-resistant penicillins (methicillin, oxacillin, cloxacillin, and flucloxacillin) were developed to treat penicillin-resistant *S. aureus* and are still used as first-line treatment. Methicillin, introduced in 1959, was the first antibiotic in this class to be used, but only 2 years later, the first case of MRSA was reported in England. The mechanism of resistance to methicillin is mediated via the mec operon, part of the *Staphylococcal* cassette chromosome mec. Resistance is conferred by the mecA gene, which codes for an altered penicillin-binding protein (PBP2a or PBP2) that has a lower affinity for binding β-lactams (penicillins, cephalosporins, and carbapenems). This allows resistance to all β-lactam antibiotics and obviates their clinical use during MRSA infections. The glycopeptide vancomycin is often deployed against MRSA. Glycopeptide resistance is mediated by acquisition of the vanA gene. The vanA gene originates from the *Enterococci* and codes for an enzyme that produces an alternative peptidoglycan to which vancomycin will not bind.

Despite the first report in 1961, MRSA generally remained an uncommon finding even in hospital settings until the 1990s, when there was an explosion in MRSA prevalence in hospitals, where it is now endemic. In the United States, 95 million people carry *S. aureus* in their noses; of these, 2.5 million (2.6% of carriers) carry MRSA.

**HOSPITAL ACQUIRED VERSUS COMMUNITY ACQUIRED**

Approximately 20% of the population carry *S. aureus* persistently, 60% are intermittent carriers, and 20% are noncarriers who rarely harbor *S. aureus*. Historically, MRSA pathogens were almost exclusively isolated from hospitals or hospital-associated facilities. However, an increasing number of MRSA cases have been reported in individuals with no known risk factors for MRSA colonization, such as admission to a hospital, surgery, contact with a MRSA-colonized patient, intravenous drug use, or previous antibiotic exposure. These isolates, termed community-acquired MRSA, have become a global concern and have been found worldwide, not only in the community setting but also in healthcare facilities. Some hospitals have reported a predominance of community-acquired MRSA isolates over hospital-acquired MRSA isolates. Community-acquired MRSA strains can reportedly interact with a human host such as other *S. aureus* strains; that is, they are most often commensals that colonize asymptotically on the mucous membranes or the skin: 25% to 35% of people have a strain of MRSA as a component of their flora at any given time.

Although “acquired” implies that the location of transmission is known, the hospital-acquired and community-acquired designations have also been used to describe the phenotypic and molecular traits of MRSA isolates. A general guide used to identify hospital-acquired versus community-acquired MRSA is resistance to certain antibiotic classes. Fluoroquinolone resistance is typically seen in hospital-acquired MRSA, whereas community-acquired MRSA is typically still susceptible. Commensal MRSA bacteria from the skin and nasopharynx are often the source of ocular infections.

The prevalence of MRSA colonization seems to vary by community: 0.1% of patients screened on admission to a hospital in Geneva, Switzerland; 2.8% of the urban poor in San Francisco, California, USA; 6.8% of homeless San Francisco youth studied in 2000; and 9.2% of Tennessee children reporting for health maintenance visits. In the U.S., historically, healthcare workers, people in nursing homes, prisoners, and people involved in contact sports were thought to be at higher risk for being colonized with MRSA. In 1 hospital in Texas, 12% of the staff were carriers of MRSA. In an Illinois emergency room, 15% of the emergency department staff were carriers. However, community-acquired MRSA is no longer a pathogen unique to certain high-risk populations such as hospital workers and inmates. Most patients presenting at an outpatient setting with a MRSA soft-tissue infection are not linked to a distinct high-risk group. An early study examining the factors associated with ocular MRSA colonization reported significant risks were long-term use of antibiotics and/or steroids and recent hospitalization.

**EPIDEMIOLOGY**

*Staphylococcus aureus* is reported to be the second most common pathogen causing bacterial keratitis across the world. Of special concern are increasing reports of postoperative MRSA infection. For example, MRSA wound infections have been reported with clear corneal phacoemulsification wounds, whereas MRSA keratitis, a serious and increasing complication following ophthalmic surgery, has been found after laser in situ keratomileusis and photorefractive keratectomy (PRK), including bilateral PRK in medical residents. Sotozono et al. reported 3 cases of MRSA keratitis after penetrating
keratoplasty, 1 case after lamellar keratoplasty, and 4 cases after epithelial transplantation for Stevens-Johnson syndrome. These and other associated data suggest that MRSA has become increasingly prevalent worldwide, as is evident from many surveillance studies. However, the University of California, San Francisco, California, USA, found that most MRSA infections are what would be considered non-severe, such as blepharitis, conjunctivitis, and dacryocystitis. In their report, only 2.4% of all ocular MRSA infections were postsurgical endophthalmitis cases.

A 2008 Finnish study examining causes of ocular infection in 2492 patients in addition to resistance patterns found S. aureus was the most common in the elderly (age >70), among whom a rapid increase in resistance of S. aureus to methicillin (MRSA) was recognized (36.8%). Coincidentally, another study published in 2008 in Japan looked at the methicillin-resistance incidence of conjunctival bacteria isolated preoperatively from 200 asymptomatic patients at 2 university hospitals. A similar rate of approximately 40.0% of Staphylococci strains (22/58 coagulase-negative Staphylococcus [CoNS], 37.9%; 4/10 S. aureus, 40.0%) were methicillin resistant. The rate of methicillin resistance for Staphylococci strains obtained from preoperative conjunctiva in the 2008 report was higher than the rate in a 1998 study by the same group (1.6% CoNS and 27.7% S. aureus isolated from preoperative conjunctiva were methicillin resistant). In 2008, a Japanese study examined the potential risk factors for harboring methicillin-resistant Staphylococcus spp. in dry-eye patients. Coagulase-negative Staphylococcus was the major aerobic conjunctival bacteria isolated from 67 patients with dry eye, and more than half (50%) of the CoNS strains isolated were methicillin resistant. This study found patients with dry eye are more likely to have fluoroquinolone-resistant methicillin-sensitive CoNS and methicillin resistant CoNS isolated from their conjunctiva than normal subjects. Some inflammatory conditions or an alteration of the normal defense system on the ocular surface of patients with dry eye may inherently cause a change in the susceptibility patterns of commensal conjunctival bacteria. The implication is that ocular surface disease should be identified and treated to reduce the risk for possible methicillin-resistant CoNS colonization.

The first case of bilateral MRSA keratitis after PRK was reported in 2003 by Solomon et al. in a person exposed in a hospital setting. They recommended more aggressive prophylaxis, maintaining high suspicion, and treating early and empirically for MRSA until proven otherwise in healthcare workers. Further recommendations included informing patients who are healthcare workers having refractive surgery of their increased risk and consider screening for MRSA by swabbing the nares. Finally, they discussed the conservative option of considering consecutive monocular treatment for keratorefractive surgery in these higher risk patients.

A study done at Stanford looked at 142 routine cataract surgery patients who were culture positive for a resistant bacteria not specific to Staphylococcus species. Diabetes, asthma, chronic blepharitis, active conjunctivitis, ocular discharge, and immunosuppressive and autoimmune disorders put patients at higher risk for drug-resistant bacteria found in the periocular normal flora. None of the patients who had commensal drug-resistant bacteria developed a postoperative infection. Therefore, resistant bacteria alone may not be a risk factor for development of an infection.

The potential for transmission of MRSA through felt-tipped marker pens is a theoretical risk. In the laboratory setting, MRSA showed heavy growth even after 10 minutes of desiccation after being dipped into culture medium with MRSA. However, in a small series (16 pens), no bacteria were cultured after 5 days of typical clinical use and reuse of the marking pens. Therefore, although a theoretical risk may be present, the clinic study did not support the risk of transmission of MRSA from felt-tip marking pens.

In a prospective multicenter study examining the specific question of bacterial resistance in 399 consecutive routine cataract surgery patients in the U.S., Staphylococcus epidermidis (62.9%) followed by S. aureus (14.0%) were the most frequently isolated organisms. Methicillin-resistant S. epidermidis accounted for 47.1% (178/378) of S. epidermidis isolates, and MRSA accounted for 29.5% (26/88) of S. aureus isolates. Methicillin-resistant Staphylococcus isolates were found in 157 of 399 (39.3%) patients, the majority (89.2%) of whom were non-healthcare workers. The likelihood of being colonized with methicillin-resistant organisms increased with age but decreased with diabetes. Being a healthcare worker was not a risk factor for colonization with methicillin-resistant organisms. In this study, age was a significant risk factor contributing to increased rates of methicillin resistance. The authors hypothesize that this increase in ocular surface colonization with resistant bacteria in adults may result from greater exposure to antibiotics, changes in meibomian gland secretions, an increased likelihood of lacrimal duct obstruction, cumulative episodes of contact with healthcare settings, or a weakened immune response. They further state that the higher prevalence of methicillin resistance with increasing age may partially explain the findings of several recent population-based studies in which older age was associated with a greater risk for endophthalmitis. The conclusion of this critical
study is that universal precautions must be followed to prevent the incidence of a methicillin-resistant infection after cataract surgery rather than a focused screening effort in those who might be considered high risk.

**PROPHYLAXIS**

**Screening Patients for MRSA Prior to Ocular Surgery**

*Staphylococcus aureus* has a diverse distribution and is capable of asymptomatically colonizing human skin and mucous membranes, including the lid and conjunctiva of the eye. An interesting study examining the practice of screening for MRSA prior to cataract surgery was reported by Rathod et al. The study looked at MRSA screening and decolonization practices in patients having routine cataract surgery in ophthalmology departments across the U.K. A survey of all ophthalmology departments in the U.K. was carried out, with 75 of 152 (49.3%) respondents returned. Sixty-three percent of units had a departmental MRSA policy. Preoperative MRSA screening was performed in 50 (66.7%) units, 3 of which screened all preoperative patients and the remainder performed selective screening. The proportion of patients screened for MRSA ranged from 0 to 100%, with a median of 2% and a mean of 9.9%. Overall, 65.3% of respondents thought their departmental policy was reasonable, although there was considerable dissatisfaction and confusion, with comments identifying lack of evidence and the need for guidelines applicable to modern cataract surgery. The authors report significant inconsistencies in preoperative MRSA screening practices in ophthalmology departments throughout the U.K. The current recommendations from the Department of Health in the U.K. suggest that ophthalmology patients do not require routine screening, although the implication according to Rathod et al. is that the recommendations appear to support the continued screening of high-risk patients.

A letter to the editor in response to the paper by Rathod et al. gives practical suggestions for screening with common sense. The authors suggest only periorbital colonization is likely to be relevant to the risk for MRSA endophthalmitis. Furthermore, they state that patients with active, clinically apparent conjunctival infection should not have elective intraocular surgery in any event. Furthermore, they present a case in which delays imposed by MRSA screening and by treatment dictums by the U.K.’s National Health Service may be an added and unintended patient safety concern, resulting in delayed access to potential visual improvement. The authors correctly state that there are no studies that show a reduced risk for postoperative endophthalmitis as a result of MRSA screening.

With the lack of findings from the U.S. prospective study on identifying possible high risk characteristics and recommendations on universal type precautions and the lack of evidence that screening for MRSA reduces the risk for postoperative infections, until further evidence shows otherwise, screening cannot be recommended as a reasonable method to reduce postoperative ocular infections from MRSA.

**DIFFERENCE BETWEEN SYSTEMIC AND OCULAR ANTIBIOTIC THERAPY**

*Staphylococcus aureus* in general and MRSA in particular continue to adapt effectively to their human hosts. Antibiotic resistance and virulence are significant growing problems. The Centers for Disease Control and Prevention (CDC) has estimated that the attack rate for invasive MRSA infections in the U.S. in a recent year was 31.8/100,000/year. This exceedingly high rate underscores the urgency of the problem and mandates the need for a major new effort to develop new therapeutic and preventive strategies.

Compared with ocular infections, the question of which systemic therapy to use as treatment for MRSA infections is more direct, despite the difficulty. Using standard microbiologic testing (minimum inhibitory concentrations) with pharmacokinetic and pharmacodynamic scientific evidence, infectious disease experts are able to choose from a handful of agents that could be effective against select MRSA strains, including fluoroquinolones, bacitracin, glycopeptides, oxazolidinones (linezolid), and increasing generations of cephalosporins. For the eye, treating MRSA is more debatable since ophthalmic standards do not exist for the extremely high concentrations achieved with topical dosing. Clinicians would not be wrong in using the systemic standards as a guide; however, treating physicians could be misguided from an effective treatment because of the incorrect assumption that the pharmacokinetic and pharmacodynamic characteristics are the same for both systemic infections and ocular applications. The University of Pittsburgh’s Campbell Laboratory has done several in vivo studies, keratitis and endophthalmitis, showing that due to the extremely high doses of topical antibiotics and the ability to apply these high doses much more frequently than parenteral dosing, it is possible to eradicate MRSA with typical agents such as cefazolin and third- and fourth-generation fluoroquinolones despite the fact that these agents would be considered ineffective, ie, deemed resistant, using typical serum standards. This implies ophthalmologists must use different standards because our
concentrations and doses are so much higher than those expected with oral or intravenous dosing. Topical fluoroquinolones are commonly used antibiotic agents in ophthalmology because of their favorable pharmacokinetics and bactericidal effectiveness for common causes of ocular infection. Recently, there have been concerns about the successful use of fourth-generation fluoroquinolones for ocular infections. In a review of antibiotic therapy, Miller reports an increase in the occurrence of fluoroquinolone-resistant *S aureus* infections, especially with MRSA. It is possible that such a resistance can develop any time the drug interacts with a large population of bacteria, including during medical and nonmedical use of the antibiotic agent. However, because the clinical use of fourth-generation fluoroquinolones for treatment and prevention of ocular infections involves a relatively small population of bacteria interacting with high tissue concentrations of topical antibiotic agent, the production of resistant mutants is less likely. The relatively low bacterial load in endophthalmitis is evidenced by the difficulty culturing from the aqueous and vitreous; the estimated detection rate is reported to be 60% by culture and gram-stain procedures. Topical ocular fluoroquinolone use is rather small compared with the total systemic fluoroquinolone use, especially considering the amount required to reach and maintain therapeutic serum levels and the many types of infections for which fluoroquinolones are used.

A study by Marshall et al. found that the source of pathogenic bacteria, such as *S aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenza*, which infect or reinfest ocular tissue, was the nasopharynx or laryngopharynx. The authors also determined that fluoroquinolone-resistant isolates of laryngopharynx-colonizing bacteria, such as *S aureus*, could be recovered from that site as well as from infected ocular tissue prior to topical fluoroquinolone ocular application. These data suggest that topical ocular administration of fourth-generation fluoroquinolones has a low probability of generating fluoroquinolone-resistant bacteria and that resistance may be more closely related to nasopharynx and laryngopharynx colonizers and frequent systemic use of fluoroquinolones. Overall, studies of fluoroquinolone tissue penetration and drug interactions with *S aureus* imply that although ophthalmology has to deal with infections involving resistant bacteria, the topical use of fluoroquinolones in the eye is unlikely to contribute significantly to the development of resistant strains during treatment. Also, it is very likely that high ocular tissue concentrations of a fourth-generation fluoroquinolone can kill a portion of *S aureus* strains classified as resistant. Romanowski et al. showed that levofloxacin-resistant *S aureus* could be killed in the rabbit cornea by applying multiple levofloxacin topical drops. Although the concern of encountering resistant bacteria is real as noted by Miller, the data do not imply that fourth-generation fluoroquinolone-resistant strains are likely to be created in an *S aureus* infection during prevention and/or treatment with fourth-generation fluoroquinolones.

Despite the low likelihood of development of resistant strains from a single typical treatment regimen, the growing rates of resistance cannot be ignored. Furthermore, studies examining the risk for development of resistance with repeated applications, specifically intravitreal injections for age-related macular degeneration, have shown unequivocally that bacterial resistance does occur with this type of unique consecutive repeated application.

Another difference in characterizing antibiotics for the eye includes the potential effects of the formulation vehicle. There has been some evidence that typical preservatives in topical preparations such as the “inactive” benzalkonium chloride may be useful in eradicating bacteria, including MRSA. These classic preservatives may improve the potency of antibiotic agents, although this has not been proven in clinical trials. Some would argue there is a dilutional effect with tears, and in vivo studies suggest a clinical trial may be warranted to more clearly describe the possible clinical effects of applying preservatives topically.

**ANTIBIOTIC SENSITIVITIES FOR MRSA**

*Staphylococcus aureus* is the most common pathogen in bacterial conjunctivitis, as reported by Adebayo et al. In this 11-year review of 20180 conjunctival bacterial cultures, isolates demonstrated high levels of resistance to tetracycline, erythromycin, and trimethoprim/sulfamethoxazole. The authors reported that moxifloxacin and gatifloxacin were the best choice for empirical broad-spectrum coverage for mucopurulent conjunctivitis; however, they reported vancomycin as the best antibiotic for MRSA coverage. They observed several significant trends in the prevalence of conjunctival bacterial isolates and in their resistance to various antibiotics over a decade at the New York Eye and Ear Infirmary, 1997 to 2008. The ratio of gram-positive to gram-negative isolates increased significantly (*P* = .004). Although fluoroquinolones are frequently used for treating conjunctivitis and other ocular infections, they observed a 6-fold increase in resistance of the gram-positive isolates group to ciprofloxacin (5% to 30%; *P* = .002), whereas the gram-negative isolates group had a less significant increase in resistance (1% to 16%; *P* = .0131). *Streptococci* and
Haemophilus influenzae maintained a consistently low level of ciprofloxacin resistance (2% to 6%). During the period of observation during this study, all isolates demonstrated low resistance to gatifloxacin and moxifloxacin (0% to 6%) until the last year of the study, 2007 to 2008, during which there was a 4- to 5-fold increase in resistance of the gram-positive isolates to moxifloxacin and gatifloxacin.

Adebayo et al.76 also reported that imipenem, moxifloxacin, and gatifloxacin had the lowest resistance rates among gram-negative isolates. The 2 aforementioned antibiotics also had the overall lowest resistance rates for gram-positive isolates after vancomycin. Staphylococcus aureus demonstrated low resistance rates to gatifloxacin and moxifloxacin (4% and 5%, respectively). These findings are similar to those of Jensen et al.77 The observation of uniformly low resistance makes fourth-generation quinolones an excellent choice for empiric broad-spectrum antibiotic coverage.

However, a 4-fold increase in the resistance of gram-positive isolates to these antibiotics in this study signaled the beginning of an increasing resistance trend. There was a 1.5-fold increase in gram-positive isolate resistance and about a 3-fold increase in trend. There was a 1.5-fold increase in gram-positive pathogen resistance to cefazolin. *Staphylococcus aureus* showed a most prominent increase in resistance, similar to the observations of Chalita et al.78

Oxacillin, a penicillinase-resistant antibiotic, exhibited an increase in resistance of 2% to 40% for *S aureus*, reflecting a significant increase in prevalence of MRSA in New York in addition to other regions.42,43,79–81 Topical trimethoprim, which in combination with polymyxin B is a commercially available agent (Polytrim), has shown some retention of in vitro activity against MRSA.80 In fact, Asbell et al. showed from 2000–2005 in 580,000 isolates, and again from 2005–2006 in 197 isolates, that trimethoprim held its efficacy in 100% and 97.6% of the methicillin-sensitive *Staphylococcus aureus* (MSSA) tested, respectively, and in 955 and 94.9% of the MRSA strains, respectively.80,81 However, it is a well-established bacteriostatic agent, with clinically insignificant penetration through intact corneal epithelium.82 Furthermore, in a retrospective case series of postoperative infectious keratitis following PKR, polymyxin B/trimethoprim used as a prophylactic agent was not able to prevent infections caused by gram-positive bacteria.83 In addition, in an experimental model of *S aureus* endophthalmitis, polymyxin B/trimethoprim was not able to prevent the clinical and microbiologic incidence.83 Therefore, regional variations may exist, and in vitro testing should be used as a guide; however, clinical judgment must incorporate many variables and may still not prevent infections.

In a New York study of the susceptibility of various *S aureus* causing infections including the eye,84 there was no resistance of any gram-positive pathogens to vancomycin, which makes it an ideal antibiotic for MRSA. The authors recommend limiting vancomycin use to MRSA to minimize the risk for resistance. However, the in vitro susceptibility tests in this study were based on serum antibiotic concentrations and may not reflect the efficacy of the antibiotic in the eye, as discussed previously.85,86 Although the World Health Organization, the United States Food and Drug Administration (FDA), the CDC, and other agencies monitor antibiotic resistance trends among bacteria causing infections of various sites within the human body, the eye is rarely a target of these investigations. In 2008, Asbell et al. reported antibiotic resistance results from 35 institutions for ocular isolates of *S aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* that had been tested for the Ocular TRUST study. Although only 16.8% of *S aureus* isolates in that study were MRSA, those isolates were frequently resistant to other antibiotics as well. The Antibiotic Resistance Monitoring in Ocular microRorganisms (ARMOR) study was initiated in 2009 to survey nationwide the resistance levels among ocular *S aureus*, CoNS, *S pneumoniae*, *H influenzae*, and *Pseudomonas aeruginosa* isolates. Isolates from patients with bacterial eye infections were collected prospectively by 34 institutions across the U.S. and were submitted to a central laboratory for inclusion in the ARMOR study. A large proportion of the *S aureus* and CoNS isolates were resistant to oxacillin/methicillin, azithromycin, or fluoroquinolones; 46.5% of *S aureus*, 58.3% of CoNS were also nonsusceptible to 2 or more antibacterial drug classes. The ARMOR study found MRSA were also statistically more likely (all *P < .0038) to be resistant to fluoroquinolones, aminoglycosides, and macrolides.87 A Japanese study showed that CoNS was the major aerobic bacteria cultured from the preoperative conjunctiva of patients having cataract surgery, and 32 (51.6%) of 62 CoNS strains isolated from the conjunctiva preoperatively were methicillin resistant. Furthermore, Hori et al.88 observed that more than half the methicillin-resistant staphylococci, including methicillin-resistant CoNS and MRSA, were resistant to levofloxacin or gatifloxacin.

In a follow-up study, Hori et al.89 found more than 80% of methicillin-resistant *Staphylococci*, including methicillin-resistant CoNS (18/22, 81.8%) and MRSA (4/4, 100%), were resistant to all fluoroquinolones studied—levofloxacin, gatifloxacin, and moxifloxacin. Because the primary objective of prophylaxis is to minimize entry of organisms into the anterior chamber and because many fluoroquinolone-resistant strains
were isolated from the conjunctiva preoperatively, Hori et al. recommend preoperative administration of antibiotic eyedrops in combination with other modalities (eg, topical povidone–iodine disinfection and/or intracameral antibiotic injection at the end of surgery) to prevent postoperative endophthalmitis.

An Indian study retrospectively reviewed 199 cases of S aureus from 1996–2008, which showed no difference in the incidence of MRSA isolated from different ocular infections. The comparison of susceptibility of MRSA and MSSA isolates with different quinolone antibiotics revealed that MRSA showed a statistically significant increase in resistance to ciprofloxacin, moxifloxacin, gatifloxacin, and ofloxacin compared with MSSA from 2006 thru 2008.

In a study that examined patients and specifically S aureus isolates that caused endophthalmitis from 1995–2008, Major et al. reported similar findings. Although all MSSA and MRSA (41%) isolates were sensitive to vancomycin in their study, fewer than half the MRSA isolates were sensitive to the four-generation fluoroquinolones. The visual acuity outcomes between MRSA-infected eyes and MSSA-infected eyes were not significantly different after resolution. This brings into question whether an infection with MRSA causes more morbidity than an infection with MSSA.

Elshan et al. reviewed Staphlococcus spp. that caused corneal ulcers (N = 157) from 2006–2007. All 21 MRSA corneal ulcer isolates were sensitive to vancomycin, linezolid, and rifampin. In addition, MRSA isolates were generally sensitive to gentamicin and tetracycline. Because colonization with MRSA is more likely to result in infection than colonization with MSSA, the use of vancomycin is recommended whenever there is clinical suspicion of MRSA, with possible use of gentamicin and bacitracin in addition or alternatives depending on the culture and sensitivity results and the clinical course.

Examining various commercially available eyelid-cleaning products, Chronister et al. reported that povidone–iodine was the most effective agent for decreasing the bacterial load that can exist on the eyelid margin. Linalool (Sterilid) was a less effective alternative. It is well known that povidone–iodine works better on contact and that the longer the contact time, the better the eradication of microbes. In this study, at 10 minutes, 99.9% of MRSA was eradicated by the povidone–iodine. At 2 minutes, which is the current U.S. FDA-approved minimum recommended length of time for the ophthalmic solution (Betadine), 95.8% was eradicated. One may consider lengthening the time of contact of the povidone–iodine to the lids and lashes, in addition to the conjunctival cul-de-sac, in patients who are known to be colonized or at high risk for MRSA to increase the efficacy of povidone–iodine.

An in vitro study examining the effects of riboflavin, ultraviolet (UV) light, and the combination of riboflavin with UV light on MRSA, the combination was effective in completely eradicating the bacteria. The combination worked much better than riboflavin alone, which did not kill any bacteria, and was better than UV light alone, which had some effect. Although this was not a clinical study nor a comparison of traditional topical therapy versus riboflavin with UV light, it does identify a possible therapy for MRSA.

Standard antibiotic regimens that assume that local strains of S aureus are sensitive to β-lactams need to be reevaluated in MRSA endemic areas. Vancomycin eyedrops can be prepared by mixing an ampule intended for intravenous use with phosphate-buffered artificial tears. The solution retains in vitro antistaphylococcal activity for at least 2 weeks without refrigeration and is usually used at a concentration of 50 mg/mL, although a concentration of 31 mg/mL has also been used successfully.

The prophylactic efficacy of intracameral vancomycin has been questioned. Studies have failed to demonstrate that vancomycin prophylaxis significantly reduces residual bacteria in the anterior chamber; however, even though there have been concerns about the use of vancomycin prophylaxis at the time of cataract surgery because of cost, potential for dilution error, and adverse effects on the eye (including cystoid macular edema), Gordon believes that ophthalmic use of vancomycin is unlikely to be a serious selection factor for promoting resistance. Libre et al. believe that the intraocular use of antibiotics is extremely unlikely to promote the development of drug-resistant organisms because the intraocular environment rarely harbors colonizing organisms. However, it is known that topical antibiotics can cause bacterial resistance at the site of application in the conjunctiva, cornea, and lids and the first report of topical ocular antibiotics inducing bacterial resistance at extraocular sites was reported in 2005. Factors that can result in selection of resistant strains include subtherapeutic dosing and extended use. Based on these data, perhaps intraocular surgeons should reevaluate the practice of using vancomycin for prophylaxis, especially as this is the current last line of defense.

RECOMMENDATIONS

How Do We Curb the Tide of MRSA?

What changes are necessary in the ophthalmologist’s practice in view of increasing bacterial resistance in the community? First, healthcare workers, including those in outpatient settings, must remove transient microorganisms from hands by using hand
wearing or hand antisepsis between all patient contacts and after contact with inanimate objects in the immediate vicinity of patients.113 Eye-lane surfaces and hand instruments should be cleaned periodically.

In many outpatient practices, it is difficult to identify MRSA patients; the establishment of electronic medical record systems may aid in this endeavor. Currently, there are no data to suggest that treatment to eradicate colonized patients with community-acquired MRSA is necessary or effective in the long term,114-116 and resistance to antibiotics used for decolonization has evolved rapidly when attempted.117-119 In the absence of a history of MRSA, a high level of suspicion is needed when patients have risk factors for nosocomial or healthcare-associated infections, including repeated intravitreal injections.

Empirical antibiotic therapy should include coverage for MRSA in endemic areas; β-lactam antibiotics may not be appropriate for empirical treatment of suspected staphylococcal infections.115 It may not be necessary to use vancomycin for coverage, because most community-acquired MRSA strains are susceptible to other antibiotics, such as bacitracin, besifloxacin, tetracycline, trimethoprim and aminoglycosides.99,115 Resistance to older quinolones is common among MRSA and occurs in as many as 90% of isolates in some hospitals.120 Chloramphenicol eyedrops have been used to treat MRSA external ocular infections,121,122 but chloramphenicol is not widely used in the U.S. because of the risk for developing aplastic anemia with its use.125,124 Prescribed treatment regimens should be appropriate in both dose and duration because inadequate dose or inadequate or excessive duration of therapy may make the development of resistance more likely.125,126 Steps should be taken to decrease the occurrence of resistant strains by adhering to guidelines advising against the routine prophylactic use of vancomycin in the hospital setting.104,127 and strong consideration should be given to eliminating the practice in other healthcare settings, such as ambulatory surgery centers.

Preoperative povidone-iodine antisepsis of the ocular surface has the most support in the literature for efficacy in preventing bacterial endophthalmitis after intraocular surgery and should be adopted. Although preoperative and postoperative topical application of broad-spectrum antibiotics and postoperative use of subconjunctival antibiotics remain common, the evidence of their efficacy is less clear128,129 and prolonged topical postoperative antibiotic administration may predispose to development of antimicrobial resistance.104,127 Currently, the strongest evidence regarding the potential efficacy for antibiotic prophylaxis surrounding cataract surgery is represented by an intracameral bolus injected at the conclusion of surgery.130 Some investigators suggest avoiding simultaneous bilateral treatment for elective ocular procedures (eg, refractive surgery) in patients colonized with MRSA or who live or work in a healthcare environment,35,36 in addition to using a fourth-generation fluoroquinolone (moxifloxacin or gatifloxacin), besifloxacin, or bacitracin for preoperative prophylaxis.39 However, choice of agent should involve regional variations in bacterial resistance patterns since in vitro studies have identified MRSA strains that are resistant to fourth-generation fluoroquinolone antibiotics moxifloxacin and gatifloxacin.131,132

New antibiotic classes with good activity against gram-positive organisms (such as ketolides and oxazolidinones) show promise in the treatment of MRSA, as may new versions of older compounds such as streptogramins, aminoglycosides such as netilmicin, and quinolones such as besifloxacin.99,134 Recent ocular antibiotic surveillance has shown the newest fluoroquinolones, besifloxacin, shows excellent activity against MRSA.137 However, antibiotic resistance even to newer antibiotics like linezolid has been reported.129 Teicoplanin, another glycopeptide antibiotic, is intrinsically less effective against S. aureus than vancomycin and is unlikely to be effective in strains with reduced vancomycin susceptibility or frank resistance.135,136 In view of increasing antimicrobial resistance worldwide, will physicians need to turn to alternative agents to treat bacterial infections as they did prior to the discovery of antibiotics? Methicillin-resistant S. aureus conjunctivitis has been treated with the antiseptic benzalkonium chloride 0.02%.137 Lysostaphin is a zinc metalloproteinase extracted from S. simulans that lyses S. aureus by disrupting its peptidoglycan layer.138,139 Lysostaphin has been shown to be effective in treating experimental MRSA keratitis and endophthalmitis.140,141 Another potentially useful enzyme, LasA protease (also called staphylolysin), is a staphyloytic endopeptidase secreted by Pseudomonas aeruginosa that also targets the peptidoglycan of S. aureus.142-144 LasA protease was comparable to vancomycin in experimental MRSA keratitis when treatment was started early and was more effective than vancomycin when treatment was started late.145 This suggests that LasA protease, unlike vancomycin, can lyse bacterial cell walls during the bacteria’s stationary phase of growth.145 Finally, a vaccine for S. aureus has been evaluated experimentally and clinically.147-149 Antimicrobial resistance to penicillin, methicillin, and vancomycin is an inevitable consequence of the selective pressure of antibiotic exposure. The need for effective prevention is as important as the need for new therapies. Despite the minor affect an individual makes on the global problem, each clinician must participate in whatever role possible to address this issue.6,130
Treatment and Prophylaxis

For the treatment of MRSA infections including blepharitis, conjunctivitis, and keratitis, clinicians should consider topical trimethoprim, gentamicin, bacitracin, besifloxacin, imipenem, and vancomycin with guidance from local microbiology laboratories.²⁷,⁹⁶ For prophylaxis of MRSA in known carriers, management with the aid of an infectious disease specialist is advisable. Efforts to clear the nares, nasopharynx, lacrimal system, and ocular surface should be made. Historically, 2 successive negative cultures are required to clear a patient as a carrier. Optimizing general health, clearing the periorcular area of any active infection or stabilizing inflammatory conditions such as ocular surface disease, and use of an effective topical antibiotic in conjunction with topical antiseptics and meticulous draping of the lids, lashes, and lacrimal system are recommended. Commercially available topical antibiotic agents include trimethoprim, gentamicin, bacitracin, and besifloxacin, with guidance from local microbiologic laboratories. Intraocular bolus at the conclusion of cataract surgery has significant evidence-based strength. Cefuroxime is not effective for MRSA; however, there is some retrospective evidence that vancomycin and moxifloxacin may be efficacious at the doses being used. The previous discussion regarding vancomycin use for prophylaxis would make its recommendations difficult at this time. Further, prospective evidence would be beneficial before a recommendation regarding intracameral moxifloxacin for MRSA prophylaxis is made. Finally, informed consent is paramount in these cases.⁶³,⁸¹,⁸⁸,⁵³,⁹⁶

SUMMARY

Community-acquired MRSA is geographically widespread; it has been reported in many regions in the U.S., as well as in Europe, Japan, India, and Australia.²⁵,¹⁵¹,¹⁵² Therefore, in the case of infections, maintain suspicion if no improvement and be informed of the local rates of MRSA.¹⁵²

Methicillin-resistant S aureus is the newest and toughest pathogen ophthalmologists have faced in the ongoing battle of ocular infections. With new standards and research into who is at risk, clinicians will be able to reduce the potential for infection from this latest enemy to the eye.

REFERENCES


**OTHER CITED MATERIAL**


California, USA, September 2009. Abstract available at: http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sessionId=020545d7-e2a1-4037-ba2d290122a59d&cKey=728f1d8b-6189-4a6b-ba11-1b95be7b65fb&mKey=%7b14EBFE7E-6F65-4D97-8CB6-F64F4347C38A%7d. Accessed July 8, 2014