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

Francis S. Mah, MD, Richard Davidson, MD, Edward J. Holland, MD, John Hovanesian, MD, Thomas John, MD, John Kanellopoulos, MD, Neda Shamie, MD, Christopher Starr, MD, David Vroman, MD, Terry Kim, MD, for the ASCRS Cornea Clinical Committee

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.

Financial Disclosure: No author has a financial or proprietary interest in any material or method mentioned.

J Cataract Refract Surg 2014; 40:1894–1908 © 2014 ASCRS and ESCRS

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.[1] 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.[2] *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*.[3] 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.[4]

Submitted: November 7, 2013.
Final revision submitted: June 18, 2014.
Accepted: June 18, 2014.

Corresponding author: Francis S. Mah, MD, Scripps Clinic, 10666 North Torrey Pines Road, MS 214, La Jolla, California 92037, USA. E-mail: mah.francis@scrippshealth.org.

http://dx.doi.org/10.1016/j.jcrs.2014.09.023
0886-3350

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.[5] 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.[6] 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.[7]

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.[8] In the United States, 95 million people carry *S aureus* in their noses; of these, 2.5 million (2.6% of carriers) carry MRSA.[9]

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*.[3] 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.[10–12] 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.[13] Some hospitals have reported a predominance of community-acquired MRSA isolates over hospital-acquired MRSA isolates.[14,15] 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 asymptomatically 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.[3]

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.[16]

The prevalence of MRSA colonization seems to vary by community: 0.1% of patients screened on admission to a hospital in Geneva, Switzerland[17]; 2.8% of the urban poor in San Francisco, California, USA[18]; 6.8% of homeless San Francisco youth studied in 2000[19]; and 9.2% of Tennessee children reporting for health maintenance visits.[20] 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.[21] In 1 hospital in Texas, 12% of the staff were carriers of MRSA.[22] In an Illinois emergency room, 15% of the emergency department staff were carriers.[23] 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.[24,25] 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.[26]

EPIDEMIOLOGY

Staphylococcus aureus is reported to be the second most common pathogen causing bacterial keratitis across the world.[27,28] Of special concern are increasing reports of postoperative MRSA infection. For example, MRSA wound infections have been reported with clear corneal phacoemulsification wounds,[29,30] whereas MRSA keratitis, a serious and increasing complication following ophthalmic surgery, has been found after laser in situ keratomileusis[31,32] and photorefractive keratectomy (PRK),[33] including bilateral PRK in medical residents.[34,35] Sotozono et al.[26] 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.[36–41] 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.[42]

A 2008 Finnish study[43] 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[44] 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).[45] 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,[45,46] 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.[45] 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.[34] 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.[40]

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),[47] 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.,[48] *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.[49–53] 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.[54–56] 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.[57–61] An interesting study examining the practice of screening for MRSA prior to cataract surgery was reported by Rathod et al.[62] 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%) questionnaires 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[63] in response to the paper by Rathod et al.[62] 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.[A,B] 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[48] and the lack of evidence that screening for MRSA reduces the risk for postoperative infections,[62] 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.[64,65]

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.[64] 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[56] and endophthalmitis,[57] 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.[66–69] Recently, there have been concerns about the successful use of fourth-generation fluoroquinolones for ocular infections. In a review of antibiotic therapy, Miller[70] 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.[71] 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.[72,73]

A study by Marshall et al.[C] found that the source of pathogenic bacteria, such as *S aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenza*, which infect or reinfect 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.[D] 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,[70] 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.[73,74]

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.[75]

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.[56]

ANTIBIOTIC SENSITIVITIES FOR MRSA

Staphylococcus aureus is the most common pathogen in bacterial conjunctivitis, as reported by Adebayo et al.[76] In this 11-year review of 20 180 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 gram-negative 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 PRK, polymyxin B/trimethoprim used as a prophylactic agent was not able to prevent infections caused by gram-positive bacteria.[35] 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.[81] reported antibiotic resistance results from 35 institutions for ocular isolates of *S aureus*, *Haemophilus influenza*, and *Streptococcus pneumonia* 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 micRorganisms (ARMOR) study was initiated in 2009 to survey nationwide the resistance levels among ocular *S aureus*, CoNS, *S pneumoniae*, *H influenza*, 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[90] and/or intracameral antibiotic injection at the end of surgery[91]) to prevent postoperative endophthalmitis.

An Indian study[92] 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.[93] 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 fourth-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.[94] 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,[95,96] 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.[97] 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.[98]

Standard antibiotic regimens that assume that local strains of *S aureus* are sensitive to β-lactams need to be reevaluated in MRSA endemic areas.[99] 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[100] and is usually used at a concentration of 50 mg/mL,[101,102] although a concentration of 31 mg/mL has also been used successfully.[103]

The prophylactic efficacy of intracameral vancomycin has been questioned.[90,104,105] Studies have failed to demonstrate that vancomycin prophylaxis significantly reduces residual bacteria in the anterior chamber[106,107]; however, even though there have been concerns about the use of vancomycin prophylaxis at the time of cataract surgery because of cost,[104] potential for dilution error,[108] and adverse effects on the eye (including cystoid macular edema),[109] Gordon[104] believes that ophthalmic use of vancomycin is unlikely to be a serious selection factor for promoting resistance. Libre et al.[110] 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[111] and the first report of topical ocular antibiotics inducing bacterial resistance at extraocular sites was reported in 2005.[112] 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

washing 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.[123,124] 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 new 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 clear[128,129] and prolonged topical postoperative antibiotic administration may predispose to development of antimicrobial resistance.[104,129] 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.[35] 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,[133] 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 fluoroquinolone, besifloxacin, shows excellent activity against MRSA.[87] 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 staphylolytic 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.[146,147] 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.[6,150]

Treatment and Prophylaxis

For the treatment of MRSA infections including blepharitis, conjunctivitis, and keratitis, clinicians should consider topical trimethoprim, gentamicin, bacitracin, besifloxacin, imipenum, and vancomycin with guidance from local microbiology laboratories.[77,96] 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 periocular 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 antisepsis 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. Intracameral 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.[63,81,88,93,96]

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

1. Mah FS. New antibiotics for bacterial infections. Ophthalmol Clin North Am 2003; 16(1):11–27
2. Ogston A. "On abscesses." [Classics in infectious diseases]. Rev Infect Dis 1984; 6:122–128
3. Kluytmans J, van Belkum A, Verbrugh H. Nasal carriage of Staphylococcus aureus: epidemiology, underlying mechanisms, and associated risks. Clin Microbiol Rev 1997; 10:505–520. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC172932/pdf/100505.pdf. Accessed July 8, 2014
4. U.S. National Institutes of Health. Experimental staph vaccine broadly protective in animal studies. NIH news release. Embargoed for release May 27, 1999. Available at: http://www.nih.gov/news/pr/may99/niaid-27.htm. Accessed July 8, 2014
5. Jevons MP. "Celbenin"-resistant staphylococci [letter]. BMJ 1961; 1:124–125. replies by GN Rolinson, R Knox, 125–126. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1952888/pdf/brmedj02876-0102b.pdf. Replies available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1952878/pdf/brmedj02876-0103.pdf. Accessed July 8, 2014
6. Chambers HF. The changing epidemiology of Staphylococcus aureus. Emerg Infect Dis 2001; 7:178–182. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2631711/pdf/11294701.pdf
7. Chang S, Sievert DM, Hageman JC, Boulton ML, Tenover FC, Downes FP, Shah S, Rudrik JT, Pupp GR, Brown WJ, Cardo D, Fridkin SK; for the Vancomycin-Resistant Staphylococcus aureus Investigative Team. Infection with vancomycin-resistant Staphylococcus aureus containing the vanA resistance gene. N Engl J Med 2003; 348:1342–1347. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa025025. Accessed July 8, 2014
8. Johnson AP, Aucken HM, Cavendish S, Ganner M, Wale MCJ, Warner M, Livermore DM, Cookson BD; the UK EARSS participants. Dominance of EMRSA-15 and -16 among MRSA causing nosocomial bacteraemia in the UK: analysis of isolates from the European Antimicrobial Resistance Surveillance System (EARSS) [letter]. J Antimicrob Chemother 2001; 48:143–144. Available at: http://jac.oxfordjournals.org/content/48/1/143.full.pdf. Accessed July 8, 2014
9. Graham P III, Lin SX, Larson EL. A U.S. population-based survey of Staphylococcus aureus colonization. Ann Intern Med 2006; 144:318–325
10. Warshawsky B, Hussain Z, Gregson DB, Alder R, Austin M, Bruckschwaiger D, Chagla AH, Daley J, Duhaime C, McGhie K, Pollett G, Potters H, Schiedel L. Hospital and community-based surveillance of methicillin-resistant Staphylococcus aureus: previous hospitalization is the major risk factor. Infect Control Hosp Epidemiol 2000; 21:724–727. Available at: http://www.jstor.org/stable/pdfplus/10.1086/501718.pdf. Accessed July 8, 2014
11. Monnet DL, MacKenzie FM, López-Lozano JM, Beyaert A, Camacho M, Wilson R, Stuart D, Gould IM. Antimicrobial drug use and methicillin-resistant Staphylococcus aureus, Aberdeen, 1996–2000. Emerg Infect Dis 2004; 10:1432–1441. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3320421/pdf/02-0694.pdf. Accessed July 8, 2014
12. Herold BC, Immergluck LC, Maranan MC, Lauderdale DS, Gaskin RE, Boyle-Vavra S, Leitch CD, Daum RS. Community-acquired methicillin-resistant Staphylococcus aureus in children with no identified predisposing risk. JAMA 1998; 279:593–598. Available at: http://jama.jamanetwork.com/data/Journals/JAMA/4549/JOC71943.pdf. Accessed July 8, 2014
13. Boyce JM. Community-associated methicillin-resistant Staphylococcus aureus as a cause of health care-associated infection. Clin Infect Dis 2008; 46:795–798. Available at: http://cid.oxfordjournals.org/content/46/6/795.full.pdf. Accessed July 8, 2014
14. Seybold U, Kourbatova EV, Johnson JG, Halvosa SJ, Wang YF, King MD, Ray SM, Blumberg HM. Emergence of

community-associated methicillin-resistant Staphylococcus aureus USA300 genotype as a major cause of health care–associated blood stream infections. Clin Infect Dis 2006; 42:647–656. Available at: http://cid.oxfordjournals.org/content/42/5/647.full.pdf. Accessed July 8, 2014

15. Popovich KJ, Weinstein RA, Hota B. Are community- associated methicillin-resistant Staphylococcus aureus (MRSA) strains replacing traditional nosocomial MRSA strains? Clin Infect Dis 2008; 46:787–794. Available at: http://cid.oxfordjournals.org/content/46/6/787.full.pdf. Accessed July 8, 2014
16. Hesje CK, Sanfilippo CM, Haas W, Morris TW. Molecular epidemiology of methicillin-resistant and methicillin-susceptible Staphylococcus aureus isolated from the eye. Curr Eye Res 2011; 36:94–102. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3021952/pdf/ncer36-094.pdf. Accessed July 8, 2014
17. Harbarth S, François P, Shrenzel J, Fankhauser-Rodriguez C, Hugonnet S, Koessler T, Huyghe A, Pittet D. Community-associated methicillin-resistant Staphylococcus aureus, Switzerland. Emerg Infect Dis 2005; 11:962–965. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3367580/pdf/04-1308.pdf. Accessed July 8, 2014
18. Charlebois ED, Bangsberg DR, Moss NJ, Moore MR, Moss AR, Chambers HF, Perdreau-Remington F. Population-based community prevalence of methicillin-resistant Staphylococcus aureus in the urban poor of San Francisco. Clin Infect Dis 2002; 34:425–433. Available at: http://cid.oxfordjournals.org/content/34/4/425.full.pdf. Accessed July 8, 2014
19. Pan ES, Diep BA, Charlebois ED, Auerswald C, Carleton HA, Sensabaugh GF, Perdreau-Remington F. Population dynamics of nasal strains of methicillin-resistant Staphylococcus aureus—and their relation to community-associated disease activity. J Infect Dis 2005; 192:811–818. Available at: http://jid.oxfordjournals.org/content/192/5/811.full.pdf. Accessed July 8, 2014
20. Creech CB II, Kernodle DS, Alsentzer A, Wilson C, Edswards KM. Increasing rates of nasal carriage of methicillin-resistant Staphylococcus aureus in healthy children. Pediatr Infect Dis J 2005; 24:617–621
21. Engelbert M, Miño de Kaspar H, Mette M, Thiel M, Ta CN, Grasbon T, Schulze-Schwering M, Klauss V, Kampik A. Intravenous treatment of experimental Staphylococcus aureus endophthalmitis: imipenem versus the combination of ceftazidime and amikacin. Graefes Arch Clin Exp Ophthalmol 2003; 241:1029–1036
22. Ibarra M, Flatt T, Van Maele D, Ahmed A, Fergie J, Purcell K. Prevalence of methicillin-resistant Staphylococcus aureus nasal carriage in healthcare workers. Pediatr Infect Dis J 2008; 27:1109–1111
23. Bisaga A, Paquette K, Sabatini L, Lovell EO. A prevalence study of methicillin-resistant Staphylococcus aureus colonization in emergency department health care workers. Ann Emerg Med 2008; 52:525–528
24. Moran GJ, Amii RN, Abrhamian FM, Talan DA. Methicillin-resistant Staphylococcus aureus in community-acquired skin infections. Emerg Infect Dis 2005; 11:928–930. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3367577/pdf/04-0641.pdf. Accessed July 8, 2014
25. Rutar T, Chambers HF, Crawford JB, Perdreau-Remington F, Zwick OM, Karr M, Diehn JJ, Cockerham KP. Ophthalmic manifestations of infections caused by the USA300 clone of community-associated methicillin-resistant Staphylococcus aureus. Ophthalmology 2006; 113:1455–1462
26. Sotozono C, Inagaki K, Fujita A, Koizumi N, Sano Y, Inatomi T, Kinoshita S. Methicillin-resistant Staphylococcus aureus and methicillin-resistant Staphylococcus epidermidis infections in the cornea. Cornea 2002; 21(suppl 2):S94–S101
27. Tuft SJ, Matheson M. In vitro antibiotic resistance in bacterial keratitis in London. Br J Ophthalmol 2000; 84:687–691. Available at: http://bjo.bmj.com/content/84/7/687.full.pdf. Accessed July 8, 2014
28. Schaefer F, Bruttin O, Zografos L, Guex-Crosier Y. Bacterial keratitis: a prospective clinical and microbiological study. Br J Ophthalmol 2001; 85:842–847. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1724042/pdf/v085p00842.pdf. Accessed July 8, 2014
29. Cosar CB, Cohen EJ, Rapuano CJ, Laibson PR. Clear corneal wound infection after phacoemulsification. Arch Ophthalmol 2001; 119:1755–1759
30. Chiang RK, Rapuano CJ. Recurrent methicillin-resistant Staphylococcus aureus wound ulcer after clear-cornea cataract surgery. CLAO J 2002; 28:109–110
31. Rudd JC, Moshirfar M. Methicillin-resistant Staphylococcus aureus keratitis after laser in situ keratomileusis. J Cataract Refract Surg 2001; 27:471–473
32. Rubinfeld RS, Negvesky GJ. Methicillin-resistant Staphylococcus aureus ulcerative keratitis after laser in situ keratomileusis. J Cataract Refract Surg 2001; 27:1523–1525
33. Förster W, Becker K, Hungermann D, Busse H. Methicillin-resistant Staphylococcus aureus after excimer laser photorefractive keratectomy. J Cataract Refract Surg 2002; 28:722–724
34. Solomon R, Donnenfeld ED, Perry HD, Biser S. Bilateral methicillin-resistant Staphylococcus aureus keratitis in a medical resident following an uneventful bilateral photorefractive keratectomy. Eye Contact Lens 2003; 29:187–189
35. Donnenfeld ED, O'Brien TP, Solomon R, Perry HD, Speaker MG, Wittpenn J. Infectious keratitis after photorefractive keratectomy. Ophthalmology 2003; 110:743–747
36. Menichitti F. Current and emerging serious Gram-positive infections. Clin Microbiol Infect 2005; 11(suppl 3):22–28. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1469-0691.2005.01138.x/pdf. Accessed July 8, 2014
37. Lowy FD. Staphylococcus aureus infections. N Engl J Med 1998; 339:520–532. Available at: http://portaldev.rti.org/10_Midas_Docs/MRSA/MRSA_Lowy_1998.pdf. Accessed July 8, 2014
38. Zinn CS, Westh H, Rosdahl VT; the Sarisa Study Group. An international multicenter study of antimicrobial resistance and typing of hospital Staphylococcus aureus from 21 laboratories in 19 countries or states. Microb Drug Resist 2004; 10:160–168
39. Tenover FC, Arbeit R, Archer G, Biddle J, Byrne S, Goering R, Hancock G, Hébert GA, Hill B, Hollis R, Jarvis WR, Kreiswirth B, Eisner W, Maslow J, McDougal LK, Miller JM, Mulligan M, Pfaller MA. Comparison of traditional and molecular methods of typing isolates of Staphylococcus aureus. J Clin Microbiol 1994; 32:407–415. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC263045/pdf/jcm00002-0147.pdf. Accessed July 8, 2014
40. Kreiswirth B, Kornblum J, Arbeit RD, Eisner W, Maslow JN, McGeer A, Low DE, Novick RP. Evidence for clonal origin of methicillin resistance in Staphylococcus aureus. Science 1993; 259:227–230
41. Ayliffe GAJ. The progressive intercontinental spread of methicillin-resistant Staphylococcus aureus. Clin Infect Dis 1997; 24(suppl 1):S74–S79. Available at: http://cid.oxfordjournals.org/content/24/Supplement_1/S74.full.pdf. Accessed July 8, 2014

42. Freidlin J, Acharya N, Lietman TM, Cevallos V, Whitcher JP, Margolis TP. Spectrum of eye disease caused by MRSA. Am J Ophthalmol 2007; 144:313–315
43. Hautala N, Koskela M, Hautala T. Major age group-specific differences in conjunctival bacteria and evolution of antimicrobial resistance revealed by laboratory data surveillance. Curr Eye Res 2008; 33:907–911
44. Kato T, Hayasaka S. Methicillin-resistant Staphylococcus aureus and methicillin-resistant coagulase-negative staphylococci from conjunctivas of preoperative patients. Jpn J Ophthalmol 1998; 42:461–465
45. Hori Y, Maeda N, Sakamoto M, Koh S, Inoue T, Tano T. Bacteriologic profile of the conjunctiva in the patients with dry eye. Am J Ophthalmol 2008; 146:729–734
46. Avunduk AM, Avunduk MC, Varnell ED, Kaufman HE. The comparison of efficacies of topical corticosteroids and nonsteroidal anti-inflammatory drops on dry eye patients: a clinical and immunocytochemical study. Am J Ophthalmol 2003; 136:593–602
47. Sim DA, Feasey N, Wren S, Breathnach A, Thompson G. Cross-infection risk of felt-tipped marker pens in cataract surgery. Eye 2009; 23:1094–1097. Available at: http://www.nature.com/eye/journal/v23/n5/pdf/eye2008214a.pdf. Accessed July 8, 2014
48. Olson R, Donnenfeld E, Bucci FA Jr, Price FW Jr, Raizman M, Solomon K, Devgan U, Trattler W, Dell S, Wallace RB, Callegan M, Brown H, McDonnell PJ, Conway T, Schiffman RM, Hollander DA. Methicillin resistance of Staphylococcus species among health care and nonhealth care workers undergoing cataract surgery. Clin Ophthalmol 2010; 4:1505–1514. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3009999/pdf/opth-4-1505.pdf. Accessed July 8, 2014
49. Fridkin SK, Hageman JC, Morrison M, Thomson Sanza L, Como-Sabetti K, Jernigan JA, Harriman K, Harrison LH, Lynfield R, Farley MM; for the Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. Methicillin-resistant Staphylococcus aureus disease in three communities. N Engl J Med 2005; 352:1436–1444. erratum, 2362. Available at: http://cryoeuro.eu:8080/download/attachments/425990/MRSAPopulationPenetration+NEMJ+CDC+2008.pdf. Accessed July 8, 2014
50. Grubeck-Loebenstein B. Changes in the aging immune system. Biologicals 1997; 25:205–208
51. Miller RA. The aging immune system: primer and prospectus. Science 1996; 273:70–74
52. Sunderkötter C, Kalden H, Luger TA. Aging and the skin immune system. Arch Dermatol 1997; 133:1256–1262
53. Woog JJ. The incidence of symptomatic acquired lacrimal outflow obstruction among residents of Olmsted County, Minnesota, 1976-2000 (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc 2007; 105:649–666. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2258133/pdf/1545-6110_v105_p649.pdf. Accessed July 8, 2014
54. West ES, Behrens A, McDonnell PJ, Tielsch JM, Schein OD. The incidence of endophthalmitis after cataract surgery among the U.S. Medicare population increased between 1994 and 2001. Ophthalmology 2005; 112:1388–1394. Available at: http://www.v2020la.org/pub/PUBLICATIONS_BY_TOPICS/Endophthalmitis/Rate%20of%20endophthamitis%20(ready).pdf. Accessed July 8, 2014
55. Hatch WV, Cernat G, Wong D, Devenyi R, Bell CM. Risk factors for acute endophthalmitis after cataract surgery: a population-based study. Ophthalmology 2009; 116:425–430
56. Romanowski EG, Mah FS, Kowalski RP, Yates KA, Gordon YJ. Benzalkonium chloride enhances the antibacterial efficacy of gatifloxacin in an experimental rabbit model of intrastromal keratitis. J Ocul Pharmacol Ther 2008; 24:380–384
57. Kowalski RP, Romanowski EG, Mah FS, Sasaki H, Fukuda M, Gordon YJ. A comparison of moxifloxacin and levofloxacin topical prophylaxis in a fluoroquinolone-resistant Staphylococcus aureus rabbit model. Jpn J Ophthalmol 2008; 52:211–216
58. Centers for Disease Control and Prevention (CDC). Methicillin-resistant Staphylococcus aureus skin or soft tissue infections in a state prison—Mississippi, 2000. MMWR Morb Mortal Wkly Rep 2001; 50:919–922. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5042a2.htm. Accessed July 8, 2014
59. Mahajan VM. Acute bacterial infections of the eye: their aetiology and treatment. Br J Ophthalmol 1983; 67:191–194. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1040006/pdf/brjopthal00159-0055.pdf. Accessed July 8, 2014
60. Groden LR, Murphy B, Rodnite J, Genvert GI. Lid flora in blepharitis. Cornea 1991; 10:50–53
61. Speaker MG, Milch FA, Shah MK, Eisner W, Kreiswirth BN. Role of external bacterial flora in the pathogenesis of acute postoperative endophthalmitis. Ophthalmology 1991; 98:639–649; discussion by J Baum, 650
62. Rathod D, Luqmani N, Webber SK, Hosein IK. Survey of meticillin-resistant Staphylococcus aureus policies in UK eye departments. J Hosp Infect 2009; 72:314–318
63. Porter LF, Khan RU, Kelly SP. Unintended consequences and MRSA screening policy [letter]. J Hosp Infect 2010; 76:275
64. Amsterdam D. Susceptibility testing of antimicrobials in liquid media. In: Lorian V, ed, Antibiotics in Laboratory Medicine, 5th ed. Philadelphia, PA, Lippincott Williams & Wilkins, 2005; 127
65. Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, Harrison LH, Lynfield R, Dumyati G, Townes JM, Craig AS, Zell ER, Fosheim GE, McDougal LK, Carey RB, Fridkin SK; for the Active Bacterial Core surveillance (ABCs) MRSA Investigators. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. JAMA 2007; 298:1763–1771. Available at: http://jama.jamanetwork.com/data/Journals/JAMA/5236/joc70110_1763_1771.pdf. Accessed July 8, 2014
66. Fukuda M, Sasaki H. Measurement of AQCmax of five different ophthalmic solutions and discussion of its new application. J Ocul Pharmacol Ther 2009; 25:351–356
67. Morlet N, Graham GG, Gatus B, McLachlan AJ, Salonikas C, Naidoo D, Goldberg I, Lam CM. Pharmacokinetics of ciprofloxacin in the human eye: a clinical study and population pharmacokinetics analysis. Antimicrob Agents Chemother 2000; 44:1674–1679. Available at: http://aac.asm.org/content/44/6/1674.full.pdf. Accessed July 8, 2014
68. Sugioka K, Fukuda M, Komoto S, Itahashi M, Yamada M, Shimomura Y. Intraocular penetration of sequentially instilled topical moxifloxacin, gatifloxacin, and levofloxacin. Clin Ophthalmol 2009; 3:553–557. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2770866/pdf/opth-3-553.pdf. Accessed July 8, 2014
69. Yağcı R, Oflu Y, Dinçel A, Kaya E, Yağcı S, Bayar B, Duman S, Bozkurt A. Penetration of second-, third-, and fourth-generation topical fluoroquinolone into aqueous and vitreous humour in a rabbit endophthalmitis model. Eye 2007;

21:990–994. Available at: http://www.nature.com/eye/journal/v21/n7/pdf/6702414a.pdf. Accessed July 8, 2014
70. Miller D. Review of moxifloxacin hydrochloride ophthalmic solution in the treatment of bacterial eye infections. Clin Ophthalmol 2008; 2:77–91. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2698721/pdf/co-2-77.pdf. Accessed July 8, 2014
71. Goldschmidt P, Degorge S, Benallaoua D, Basli E, Batellier L, Boutboul S, Allouch C, Borderie V, Laroche L, Chaumeil C. New test for the diagnosis of bacterial endophthalmitis. Br J Ophthalmol 2009; 93:1089–1095
72. Rogues AM, Dumartin C, Amadéo B, Venier AG, Marty N, Parneix P, Gachie JP. Relationship between rates of antimicrobial consumption and the incidence of antimicrobial resistance in Staphylococcus aureus and Pseudomonas aeruginosa isolates from 47 French hospitals. Infect Control Hosp Epidemiol 2007; 28:1389–1395. Available at: http://www.jstor.org/stable/10.1086/523280. Accessed July 8, 2014
73. Committee on Infectious Diseases. The use of systemic fluoroquinolones. Pediatrics 2006; 118:1287–1292. Available at: http://pediatrics.aappublications.org/content/118/3/1287.full.pdf. Accessed July 8, 2014
74. Balzli CL, Caballero AR, Tang A, Weeks AC, O'Callaghan RJ. Penetration and effectiveness of prophylactic fluoroquinolones in experimental methicillin-sensitive or methicillin-resistant Staphylococcus aureus anterior chamber infections. J Cataract Refract Surg 2010; 36:2160–2167
75. Milder E, Vander J, Shah C, Garg S. Changes in antibiotic resistance patterns of conjunctival flora due to repeated use of topical antibiotics after intravitreal injection. Ophthalmology 2012; 119:1420–1424
76. Adebayo A, Parikh JG, McCormick SA, Shah MK, Huerto RS, Yu G, Milman T. Shifting trends in in vitro antibiotic susceptibilities for common bacterial conjunctival isolates in the last decade at the New York Eye and Ear Infirmary. Graefes Arch Clin Exp Ophthalmol 2011; 249:111–119
77. Jensen HG, Felix C; the In Vitro Antibiotic Testing Group. In vitro antibiotic susceptibilities of ocular isolates in North and South America. Cornea 1998; 17:79–87
78. Chalita MR, Höfling-Lima AL, Paranhos A Jr, Schor P, Belfort R Jr. Shifting trends in in vitro antibiotic susceptibilities for common ocular isolates during a period of 15 years. Am J Ophthalmol 2004; 137:43–51
79. Cavuoto K, Zutshi D, Karp CL, Miller D, Feuer W. Update on bacterial conjunctivitis in South Florida. Ophthalmology 2008; 115:51–56
80. Asbell PA, Sahm DF, Shaw M, Draghi DC, Brown NP. Increasing prevalence of methicillin resistance in serious ocular infections caused by Staphylococcus aureus in the United States: 2000 to 2005. J Cataract Refract Surg 2008; 34:814–818
81. Asbell PA, Colby KA, Deng S, McDonnell P, Meisler DM, Raizman MB. Ocular TRUST: nationwide antimicrobial susceptibility patterns in ocular isolates. Am J Ophthalmol 2008; 145:951–958
82. Osher RH, Amdahl LD, Cheetham JK. Antimicrobial efficacy and aqueous humor concentration of preoperative and postoperative topical trimethoprim/polymyxin B sulfate versus tobramycin. J Cataract Refract Surg 1994; 20:3–8
83. Kowalski RP, Romanowski EG, Shanks RMQ, Mah FS. The comparison of fluoroquinolones to nonfluoroquinolone antibacterial agents for the prevention of endophthalmitis in a rabbit model. J Ocul Pharmacol Ther 2012; 28:604–608
84. Sakoulas G, Moellering RC Jr. Increasing antibiotic resistance among methicillin-resistant Staphylococcus aureus strains. Clin Infect Dis 2008; 46(suppl 5):S360–S367. Available at: http://cid.oxfordjournals.org/content/46/Supplement_5/S360.full.pdf. Accessed July 8, 2014
85. Baum J, Barza M. The evolution of antibiotic therapy for bacterial conjunctivitis and keratitis: 1970–2000. Cornea 2000; 19:659–672
86. Block SL, Hedrick J, Tyler R, Smith A, Findlay R, Keegan E, Stroman DW. Increasing bacterial resistance in pediatric acute conjunctivitis (1997–1998). Antimicrob Agents Chemother 2000; 44:1650–1654. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC89927/pdf/ac001650.pdf. Accessed July 8, 2014
87. Haas W, Pillar CM, Torres M, Morris TW, Sahm DR. Monitoring antibiotic resistance in ocular microorganisms: results from the Antibiotic Resistance Monitoring in Ocular MicRorganisms (ARMOR) 2009 surveillance study. Am J Ophthlamol 2011; 152:567–574.e3
88. Hori Y, Maeda N, Sakamoto M, Inoue T, Tano Y. Fluoroquinolone-resistant bacteria and methicillin-resistant Staphylococci from normal preoperative conjunctiva. J Cataract Refract Surg 2008; 34:711–712
89. Hori Y, Nakazawa T, Maeda N, Sakamoto M, Yokokura S, Kubota A, Inoue T, Nishida K, Tano Y. Susceptibility comparisons of normal preoperative conjunctival bacteria to fluoroquinolones. J Cataract Refract Surg 2009; 35:475–479
90. Ciulla TA, Starr MB, Masket S. Bacterial endophthalmitis prophylaxis for cataract surgery; an evidence-based update. Ophthalmology 2002; 109:13–24
91. Barry P, Seal DV, Gettinby G, Lees F, Peterson M, Revie CW; for the ESCRS Endophthalmitis Study Group. ESCRS study of prophylaxis of postoperative endophthalmitis after cataract surgery; preliminary report of principal results from a European multicenter study. J Cataract Refract Surg 2006; 32:407–410; erratum, 709
92. Bagga B, Reddy AK, Garg P. Decreased susceptibility to quinolones in methicillin-resistant Staphylococcus aureus isolated from ocular infections at a tertiary eye care centre [letter]. Br J Ophthalmol 2010; 94:1407–1408
93. Major JC Jr, Engelbert M, Flynn HW Jr, Miller D, Smiddy WE, Davis JL. Staphylococcus aureus endophthalmitis: antibiotic susceptibilities, methicillin resistance, and clinical outcomes. Am J Ophthalmol 2010; 149:278–283
94. Elsahn AF, Yildiz EH, Jungkind DL, Abdalla YF, Erdurmus M,Cremona FA, Rapuano CJ, Hammersmith KM, Cohen EJ. In vitro susceptibility patterns of methicillin-resistant Staphylococcus aureus and coagulase-negative Staphylococcus corneal isolates to antibiotics. Cornea 2010; 29:1131–1135
95. Muder RR, Brennen C, Wagener MM, Vickers RM, Rihs JD, Hancock GA, Yee YC, Miller JM, Yu VL. Methicillin-resistant Staphylococcal colonization and infection in a long-term care facility. Ann Intern Med 1991; 114:107–112
96. Leman R, Alvarado-Ramy F, Pocock S, Barg N, Kellum M, McAllister S, Cheek J, Kuehnert M. Nasal carriage of methicillin resistant Staphylococcus aureus in an American Indian population. Infect Control Hosp Epidemiol 2004; 25:121–125. Available at: http://www.jstor.org/stable/pdfplus/10.1086/502361.pdf. Accessed July 8, 2014
97. Chronister DR, Kowalski RP, Mah FS, Thompson PP. An independent in vitro comparison of povidone iodine and SteriLid®. J Ocul Pharmacol Ther 2010; 26:277–280
98. Schrier A, Greebel G, Attia H, Trokel S, Smith EF. In vitro antimicrobial efficacy of riboflavin and ultraviolet light on Staphylococcus aureus, methicillin-resistant Staphylococcus aureus, and pseudomonas aeruginosa. J Refract Surg 2009; 25:S799–S802

99. Fraise AP. Guidelines for the control of methicillin-resistant Staphylococcus aureus. J Antimicrob Chemother 1998; 42:287–289. Available at: http://jac.oxfordjournals.org/content/42/3/287.full.pdf. Accessed July 8, 2014
100. Fleischer AB, Hoover DL, Khan JA, Parisi JT, Burns RP. Topical vancomycin formulation for methicillin-resistant Staphylococcus epidermidis blepharoconjunctivitis. Am J Ophthalmol 1986; 101:283–287
101. Khan JA, Hoover D, Ide CH. Methicillin-resistant Staphylococcus epidermidis blepharitis. Am J Ophthalmol 1984; 98:562–565
102. Goodman DF, Gottsch JD. Methicillin-resistant Staphylococcus epidermidis keratitis treated with vancomycin. Arch Ophthalmol 1988; 106:1570–1571
103. Ross J, Abate MA. Topical vancomycin for the treatment of Staphylococcus epidermidis and methicillin-resistant Staphylococcus aureus conjunctivitis. DICP 1990; 24:1050; 1053
104. Gordon YJ. Vancomycin prophylaxis and emerging resistance: are ophthalmologists the villains? The heroes? Am J Ophthalmol 2001; 131:371–376
105. American Academy of Ophthalmology and the Centers for Disease Control and Prevention Task Force. The prophylactic use of vancomycin for intraocular surgery Quality of Care Publication number 515. San Francisco, CA, American Academy of Ophthalmology, 1999; Available at: http://www.aaofoundation.org/hoskins/QEC-Content-Display.cfm?fuseaction=display&link=e2b9782e-26d2-47a0-9211-4b0ed4d91ae8&section=Compendium. Accessed July 8, 2014
106. Ferro JF, de-Pablos M, Logroño MJ, Guisasola L, Aizpuru F. Postoperative contamination after vancomycin and gentamicin during phacoemulsification. Arch Ophthalmol 1997; 115:165–170
107. Feys J, Salvanet-Bouccara A, Edmond JP, Dublanchet A. Vancomycin prophylaxis and intraocular contamination during cataract surgery. J Cataract Refract Surg 1997; 23:894–897
108. Fry LL. Vancomycin dilution error. J Cataract Refract Surg 2005; 31:1674
109. Axer-Siegel R, Stiebel-Kalish H, Rosenblatt I, Strassmann E, Yassur Y, Weinberger D. Cystoid macular edema after cataract surgery with intraocular vancomycin. Ophthalmology 1999; 106:1660–1664
110. Libre PE, Della-Latta P, Chin NX. Intracameral antibiotic agents for endophthalmitis prophylaxis; a pharmacokinetic model. J Cataract Refract Surg 2003; 29:1791–1794
111. Hwang DG. Fluoroquinolone resistance in ophthalmology and the potential role for newer ophthalmic fluoroquinolones. Surv Ophthalmol 2004; 49(suppl 2):S79–S83
112. Gaynor BD, Chidambaram JD, Cevallos V, Miao Y, Miller K, Jha HC, Bhatta RC, Chaudhary JSP, Osaki Holm S, Whitcher JP, Holbrook KA, Fry AM, Lietman TM. Topical ocular antibiotics induce bacterial resistance at extraocular sites. Br J Ophthalmol 2005; 89:1097–1099. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1772818/pdf/bjo08901097.pdf. Accessed July 8, 2014
113. Boyce JM, Pittet D. Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Infect Control Hosp Epidemiol 2002; 23(suppl 12):S3–S40. Available at: http://www.jstor.org/stable/pdfplus/10.1086/503164.pdf. Accessed July 8, 2014
114. Brumfitt W, Hamilton-Miller J. Methicillin-resistant Staphylococcus aureus. N Engl J Med 1989; 320:1188–1196
115. Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J, Johnson SK, Vandenesch F, Fridkin S, O'Boyle C, Danila RN, Lynfield R. Comparison of community- and health care–associated methicillin-resistant Staphylococcus aureus infection. JAMA 2003; 290:2976–2984. Available at: http://jama.jamanetwork.com/data/Journals/JAMA/4907/JOC31009.pdf. Accessed July 8, 2014
116. Wertheim HFL, Vos MC, Ott A, Voss A, Kluytmans JAJW, Vandenbroucke-Grauls CMJE, Meester MHM, van Keulen PHJ, Verbrugh HA. Mupirocin prophylaxis against nosocomial Staphylococcus aureus infections in nonsurgical patients; a randomized study. Ann Intern Med 2004; 140:419–426
117. Miller MA, Dascal A, Portnoy J, Mendelson J. Development of mupirocin resistance among methicillin-resistant Staphylococcus aureus after widespread use of nasal mupirocin ointment. Infect Control Hosp Epidemiol 1996; 17:811–813
118. Torvaldsen S, Roberts C, Riley TV. The continuing evolution of methicillin-resistant Staphylococcus aureus in Western Australia. Infect Control Hosp Epidemiol 1999; 20:133–135. Available at: http://www.jstor.org/stable/pdfplus/10.1086/501594.pdf. Accessed July 8, 2014
119. Vasquez JE, Walker ES, Franzus BW, Overbay BK, Reagan DR, Sarubbi FA. The epidemiology of mupirocin resistance among methicillin-resistant Staphylococcus aureus at a Veterans' Affairs Hospital. Infect Control Hosp Epidemiol 2000; 21:459–464. Available at: http://www.jstor.org/stable/pdfplus/10.1086/501788.pdf. Accessed July 8, 2014
120. Diekema DJ, Pfaller MA, Schmitz FJ, Smayevsky J, Bell J, Jones RN, Beach M; the SENTRY Participants Group. Survey of infections due to Staphyoccocal species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997–1999. Clin Infect Dis 2001; 32(suppl 2):S114–S132. Available at: http://cid.oxfordjournals.org/content/32/Supplement_2/S114.full.pdf. Accessed July 8, 2014
121. Shanmuganathan VA, Armstrong M, Buller A, Tullo AB. External ocular infections due to methicillin-resistant Staphylococcus aureus (MRSA). Eye 2005; 19:284–291. Available at: http://www.nature.com/eye/journal/v19/n3/pdf/6701465a.pdf. Accessed July 8, 2014
122. Fukuda M, Ohashi H, Matsumoto C, Mishima S, Shimomura Y. Methicillin-resistant Staphylococcus aureus and methicillin-resistant coagulase-negative Staphylococcus ocular surface infection; efficacy of chloramphenicol eye drops. Cornea 2002; 21(suppl 2):S86–S89
123. Fraunfelder FT, Bagby GC Jr, Kelly DJ. Fatal aplastic anemia following topical administration of ophthalmic chloramphenicol. Am J Ophthalmol 1982; 93:356–360
124. Doona M, Walsh JB. Use of chloramphenicol as topical eye medication: time to cry halt? [editorial] BMJ 1995; 310:1217–1218. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2549610/pdf/bmj00592-0007.pdf. Accessed July 8, 2014
125. Muto CA, Jernigan JA, Ostrowsky BE, Richet HM, Jarvis WR, Boyce JM, Farr BM. SHEA guideline for preventing nosocomial transmission of mulitdrug-resistant strains of Staphylococcus aureus and Enterococcus. Infect Control Hosp Epidemiol 2003; 24:362–386. Available at: http://www.jstor.org/stable/pdfplus/10.1086/502213.pdf. Accessed July 8, 2014
126. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993; 37:1073–1081. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC187901/pdf/aac00027-0175.pdf. Accessed July 8, 2014

127. Centers for Disease Control and Prevention. Recommendations for preventing the spread of vancomycin resistance. Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 1995; 44(RR–12):1–13. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00039349.htm. Accessed July 8, 2014
128. Kessler E, Ohman DE. Staphylolysin. In: Barrett AJ, Rawlings ND, Woessner JF, eds, Handbook of Proteolytic Enzymes. London, UK, Academic Press, 1998; 1476–1478
129. Kowalski RP, Karenchak LM, Romanowski EG. Infectious disease: changing antibiotic susceptibility. Ophthalmol Clin North Am 2003; 16(1):1–9
130. Gower EW, Lindsley K, Nanji AA, Leyngold I, McDonnell PJ. Perioperative antibiotics for prevention of acute endophthalmitis after cataract surgery. Cochrane Database Syst Rev 2013; (7):CD006364. Summary available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006364.pub2/pdf/abstract. Accessed July 8, 2014
131. Ling ML, Tan PL. In vitro activity of moxifloxacin against local bacterial isolates. Ann Acad Med Singapore 2001; 30:607–610
132. Abb J. In vitro activity of linezoid, quinupristin-dalfopristin, vancomycin, teicoplanin, moxifloxacin and mupirocin against methicillin-resistant Staphylococcus aureus: comparative evaluation by the E test and a broth microdilution method. Diagn Microbiol Infect Dis 2002; 43:319–321
133. Michel M, Gutmann L. Methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci: therapeutic realities and possibilities. Lancet 1997; 349:1901–1906
134. Panagea S, Perry JD, Gould FK. Should clindamycin be used as treatment of patients with infections caused by erythromycin resistant staphylococci? [letter] J Antimicrob Chemother 1999; 44:581–582. Available at: http://jac.oxfordjournals.org/content/44/4/581.full.pdf. Accessed July 8, 2014
135. Pillai SK, Sakoulas G, Wennersten C, Eliopoulos GM, Moellering RC Jr, Ferraro MJ, Gold HS. Linezolid resistance in Staphylococcus aureus: characterization and stability of resistant phenotype. J Infect Dis 2002; 186:1603–1607. Available at: http://jid.oxfordjournals.org/content/186/11/1603.full.pdf. Accessed July 8, 2014
136. Hiramatsu K, Aritaka N, Hanaki H, Kawasaki S, Hosoda Y, Hori S, Fukuchi Y, Kobayashi I. Dissemination in Japanese hospitals of strains of Staphylococcus aureus heterogeneously resistant to vancomycin. Lancet 1997; 350:1670–1673
137. Linden PK. Clinical implications of nosocomial gram-positive bacteremia and superimposed antimicrobial resistance. Am J Med 1998; 104(issue 5, suppl 1):24S–33S
138. Horii T, Futamura N, Suzuki Y. Antiseptic treatment of methicillin-resistant Staphylococcus aureus conjunctivitis [letter]. J Infect 2001; 42:166–169
139. Schindler CA, Schuhardt VT. Lysostaphin: a new bacteriolytic agent for the Staphylococcus. Proc Natl Acad Sci U S A 1964; 51:414–421. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC300087/pdf/pnas00177-0054.pdf. Accessed July 8, 2014
140. Sloan GL, Robinson JM, Kloos WE. Identification of "Staphylococcus staphylolyticus" NRRL B-2628 as a biovar of Staphylococcus simulans. Int J Syst Bacteriol 1982; 32:170–174. Available at: http://ijs.sgmjournals.org/content/32/2/170.full.pdf. Accessed July 8, 2014
141. Dajcs JJ, Hume EBH, Moreau JM, Caballero AR, Cannon BM, O'Callaghan RJ. Lysostaphin treatment of methicillin-resistant Staphylococcus aureus keratitis in the rabbit. Invest Ophthalmol Vis Sci 2000; 41:1432–1437. Available at: http://www.iovs.org/content/41/6/1432.full.pdf. Accessed July 8, 2014
142. Dajcs JJ, Thibodeaux BA, Hume EBH, Zhang X, Sloop GD, O'Callaghan RJ. Lysostaphin is effective in treating methicillin-resistant Staphylococcus aureus endophthalmitis in the rabbit. Curr Eye Res 2001; 22:451–457
143. Kessler E, Safrin M, Olson JC, Ohman DE. Secreted LasA protease of Pseudomonas aeruginosa is a staphylolytic protease. J Biol Chem 1993; 268:7503–7508. Available at: http://www.jbc.org/content/268/10/7503.full.pdf. Accessed July 8, 2014
144. Kessler E. β-lytic endopeptidases. Meth Enzymol 1995; 248:740–756
145. Barequet IS, Ben Simon GJ, Safrin M, Ohman DE, Kessler E. Pseudomonas aeruginosa LasA protease in treatment of experimental staphylococcal keratitis. Antimicrob Agents Chemother 2004; 48:1681–1687. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC400535/pdf/0700-03.pdf. Accessed July 8, 2014
146. Callegan MC, Hill JM, Insler MS, Hobden JA, O'Callaghan RJ. Methicillin-resistant Staphylococcus aureus keratitis in the rabbit: therapy with ciprofloxacin, vancomycin, and cefazolin. Curr Eye Res 1992; 11:1111–1119
147. Fattom AI, Sarwar J, Ortiz A, Naso RA. Staphylococcus aureus capsular polysaccharide (CP) vaccine and CP-specific antibodies protect mice against bacterial challenge. Infect Immun 1996; 64:1659–1665. Available at: http://iai.asm.org/content/64/5/1659.full.pdf. Accessed July 8, 2014
148. Lee JC, Park JS, Shepherd SE, Carey V, Fattom A. Protective efficacy of antibodies to the Staphylococcus aureus type 5 capsular polysaccharide in a modified model of endocarditis in rats. Infect Immun 1997; 65:4146–4151. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC175596/pdf/654146.pdf. Accessed July 8, 2014
149. Shinefield H, Black S, Fattom A, Horwith G, Rasgon S, Ordonez J, Yeoh H, Law D, Robbins JB, Schneerson R, Muenz L, Fuller S, Johnson J, Fireman B, Alcorn H, Naso R. Use of a Staphylococcus aureus conjugate vaccine in patients receiving hemodialysis. N Engl J Med 2002; 346:491–496. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa011297. Accessed July 8, 2014
150. Blomquist PH. Methicillin-resistant Staphylococcus aureus infections of the eye and orbit (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc 2006; 104:322–345. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1809917/pdf/1545-6110_v104_p322.pdf. Accessed July 8, 2014
151. Weber JT. Community-associated methicillin-resistant Staphylococcus aureus. Clin Infect Dis 2005; 41(suppl 4):S269–S272. Available at: http://cid.oxfordjournals.org/content/41/Supplement_4/S269.full.pdf. Accessed July 8, 2014
152. Shome D, Jain V, Natarajan S, Agrawal S, Shah K. Community-acquired methicillin-resistant Staphylococcus aureus (CAMRSA)—a rare cause of fulminant orbital cellulitis. Orbit 2008; 27:179–181

OTHER CITED MATERIAL

A. Alcon Laboratories, Inc. Betadine 5% sterile ophthalmic prep solution (povidone-iodine ophthalmic solution) (0.5% available iodine). Package Insert. Available at: http://ecatalog.alcon.com/PI/Betadine5_us_en.pdf. Accessed July 8, 2014
B. Advanced Vision Research. SteriLid Eyelid Cleanser. Available at: http://www.theratears.com/sterilid.php. Accessed July 8, 2014
C. Marshall B, Cupp G, Foster K, McLean C, Cockrum P, Lichtenstein S, De Leon L, Heller W, Levy S, Stroman DW, "Moxifloxacin Treatment of Conjunctivitis: Microbial Effects Beyond the Eye," poster presented at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco,

California, USA, September 2009. Abstract available at: Abstract available at: http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=020545d7-e2a1-4037-bb42-6ad290f2a59d&cKey=728f1d08-6189-4a6b-ba11-1b95be7b65fb&mKey=%7b14EBFE7E-6F65-4D97-8CB6-F64F4347C38A%7d. Accessed July 8, 2014

D. Romanowski EG, Kowalski RP, Mah FS, Shanks RMQ, Gordon YJ, "The Evaluation of Levofloxacin 1.5% in the Treatment of Levofloxacin-Susceptible and Resistant Staphylococcus aureus and Pseudomonas aeruginosa in Rabbit Keratitis Models," presented at the 43rd annual meeting of the Ocular Microbiology and Immunology Group, San Francisco, California, USA, October 2009. Abstract available at: http://eyemicrobiology.upmc.com/2009%20Abstracts/2009%20OMIG%20Abstract%2015.html. Accessed July 8, 2014