Methicillin-Resistant *Staphylococcus aureus* and the Eye: Current Concepts and Management Strategies

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Published online: 30 October 2013
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Abstract Methicillin-resistant *Staphylococcus aureus* (MRSA) remains one of the most important causes of nosocomial infections worldwide. This review explores the history and epidemiology of MRSA infections with a detailed analysis of its molecular subtyping, target populations, virulence factors, and modes of transmission. In addition, it specifically discusses the spectrum of eye diseases caused by MRSA, reviews the current ophthalmic literature, addresses the controversy regarding ophthalmic antibiotic resistance to MRSA, and examines alternative treatment strategies.

Keywords Methicillin-resistant *Staphylococcus aureus* · MRSA · Infection · Eye

Introduction

Staphylococcus aureus is among the most important and commonly isolated human bacterial pathogens. Infections caused by *Staphylococcus aureus* range from minor skin and soft tissue infections to life-threatening systemic infections. *Staphylococcus aureus* is also a leading cause of ocular infections include conjunctivitis, keratitis and endophthalmitis [1, 2, 3, 4, 5].

Traditionally, methicillin-resistant *Staphylococcus* (MRSA) was almost exclusively associated with hospitals or hospital associated healthcare facilities, but its prevalence has increased in otherwise healthy patients without identifiable risk factors,

such as admission to a hospital, intravenous drug use, or prior antibiotic exposure [6, 7]. Such infections termed “community-associated” (CA) MRSA were clinically, microbiologically, and genetically different from healthcare-associated (HA) strains of MRSA. However, the distinction between the strains is blurring, as CA strains have migrated into the institutional setting [8, 9, 10, 11].

Staphylococcal aureus

Staphylococcal aureus is a facultative anaerobic Gram-positive cocci bacterium. Staphylococci are widespread in nature with their major habitat being skin and mucus membranes. The genome of *S. aureus* consists of a circular chromosome of approximately 2.8 Mb predicted to carry ~2,500 genes [12, 13]. Genes governing virulence and antibiotic resistance reside on both the chromosome and extrachromosomal elements [14]. These genes may be transferred between other *S. aureus* strains or other bacterial species via extrachromosomal elements [15].

MRSA History

Following the introduction of penicillin in the 1940s, the first antimicrobial drug to show effectiveness against staphylococcal infections, *S. aureus* developed penicillin resistance within a few months [16]. The molecular determinant responsible for penicillin resistance was identified as a plasmid-encoded β -lactamase gene capable of cleaving the β -lactam ring of penicillin [17, 18]. Methicillin, a semisynthetic derivative of penicillin that is resistant to cleavage by β -lactamase, was introduced for clinical use in 1959. Soon after, infections by β -lactamase

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producing penicillin-resistant strains sharply declined [19]. However, within 2 years following the introduction of methicillin, resistant strains were isolated in hospitals in the United Kingdom and subsequently in the United States [19]. Soon after, MRSA became endemic worldwide [13].

The term MRSA is used loosely, since methicillin, in the strict sense, is not an antibiotic in current clinical use. A more contemporary definition incorporates both minimum inhibitory concentration (MIC) and molecular criteria. Intrinsic resistance to methicillin and similar antibiotics through the acquisition of modified penicillin binding proteins is a major distinction for the MRSA phenotype [20•, 21].

Epidemiology of MRSA

Methicillin resistance in staphylococci is associated with the acquisition of a mobile genetic element (MGE) called the staphylococcal cassette chromosome *mec* (SCC*mec*) [11••, 22, 23]. SCC*mec* is a DNA fragment ranging from 21 to 67 kb in size depending on the SCC*mec* type [24].

For most of the past 50 years, MRSA was considered to be mostly a nosocomial pathogen with a limited number of clonal backgrounds causing serious infections in individuals with HA risk factors. HA-MRSA are among the most common causes of nosocomial infections including intravenous catheter associated infections, ventilator associated pneumonias, and surgical wound infections. In addition MRSA are the most common cause of skin and soft tissue infections in the United States [25, 26].

In the 1990s, reports of de novo CA-MRSA infections among healthy individuals began to appear in the literature and were found to have genetically distinct lineages unrelated to existing HA-MRSA strains [11••, 27]. The first case of CA-MRSA was reported in 1993 in a remote part of Western Australia lacking any close healthcare facility [28]. Shortly thereafter, CA-MRSA appeared in the USA, causing the deaths of four children from rural Minnesota and North Dakota (CDC [29]). Since that time, numerous lineages of CA-MRSA emerged across the globe [9, 10••, 1, 11••]. The history of the onset of CA-MRSA in the US has been reviewed elsewhere in great detail and is beyond the scope of this article [26, 30–32].

These highly successful CA-MRSA clones have invaded the healthcare setting and are increasingly being implicated in nosocomial infections. Mathematical models appear to predict that they will ultimately displace traditional HA-MRSA strains in the healthcare setting [23, 30]. A high number of CA-MRSA infections are being observed in the USA, but also in increasing frequency in other parts of the world, reaching pandemic proportions [23, 30, 33]. The fact that the CA-MRSA epidemic is particularly severe in

the USA is likely due to single epidemic clone USA300. The USA-300 isolate appears to have enhanced virulence as well as an enhanced capacity to colonize multiple body sites and to survive on environmental surfaces [23, 28, 30, 34, 35].

The absolute definitions of CA-MRSA and HA-MRSA are the subject of controversy. According to the current definition, CA-MRSA infections are those for which the onset of infection is within 48 h of admission to the hospital with no previous history of hospitalization in the past year, whereas HA-MRSA is defined by the onset of infection occurring after 48 h of hospital admission [33]. The most contemporary definitions now incorporate both MIC and molecular criteria. Consequently, traditional distinctions between HA-MRSA and CA-MRSA based on clinical epidemiology and susceptibility are becoming less apparent [9]. Currently, an increasing number of reports from the USA and abroad indicate that CA-MRSA isolates are gradually replacing HA-MRSA in hospitals [20•, 35].

Molecular Typing of MRSA

A unique feature of the worldwide pandemic of MRSA infections has been the discrete number of staphylococcal clones associated with these events [27]. Unlike the diversity of strains seen with methicillin-sensitive *S. aureus*, the MRSA outbreaks have been limited to a relatively small number of lineages. Overtime, these lineages have evolved, accumulating mutations that alter their gene expression and function. In addition, new genetic elements obtained via horizontal gene exchange have allowed the MRSA to alter animal species specificity, the nature of their invasive infections, and, most importantly, the type of antimicrobial resistance associated with the strains [36].

The precise molecular typing methods employed to categorize *S. aureus* and the clonal subtypes are beyond the scope of this review. The four primary methods used internationally are pulsed-field gel electrophoresis (PFGE), multilocus sequence typing, *spa* typing, and SCC*mec* typing for MRSA [28, 37–39]. PFGE is a genotyping or genetic fingerprinting method commonly considered a gold standard in epidemiological studies of pathogenic organisms. It indexes variation that accumulates rapidly, and is particularly appropriate for studies of outbreaks or short-term epidemiologic studies [37]. The PFGE database in the USA classifies major *S. aureus* clones as USA100, USA200, USA300, and so on. Well-known international designations include EMRSA (United Kingdom), WAMRSA (Western Australia), and CMRSA (Canada) [11••]. Although current typing methods are highly useful for tracking *S. aureus* outbreaks, and provide important information for our understanding of pathogen evolution,

they index variation at a relatively small number of nucleotides. Whole-genome sequencing approaches have the ability to provide the full extent of genetic diversity among isolates, and this method will become increasingly employed in the future [26].

Target Populations and Transmission

Staphylococcus aureus is a frequent asymptomatic colonizer of humans. Roughly a third of the human population carries *S. aureus* primarily in the nares, nasopharynx, groin, and perineum [40, 41]. The occurrence of nasal MRSA colonization in the human population is estimated to be about 1.5 %, of which roughly one in six carries a CA-MRSA strain [42, 43]. There are several risk factors for the acquisition of a MRSA infection. Most commonly, an individual is at a high risk for infection from his or her own colonizing strain [44]. Poor personal hygiene and a compromised skin barrier are believed to play important roles in CA infections, while underlying conditions such as a compromised immune system increase the risk for MRSA infection in hospital infections.

MRSA is prevalent in healthcare workers, and cumulative evidence suggests they may serve as a reservoir for the spread of HA-MRSA infections in hospitals [20•, 28, 45]. MRSA has been increasingly associated with livestock-associated (LA-MRSA) infections over the last four decades [46–49]. Recent reports have shown LA-MRSA strains infecting livestock-associated workers [50] and the transmission of USA100, -300, and -500 strains between humans and their companion animals [46, 50–53]. The recent breach of the genus barrier by strains of LA-MRSA indicates that livestock may serve as an additional reservoir for human infections [20•, 46].

The target population for MRSA infections is diverse. Groups at high risk for CA-MRSA include prison inmates [54], military personnel [54], athletes [55], and IV drug users [54]. In addition, the elderly, children [56], patients with indwelling medical devices [57], and people with underlying disease conditions, including diabetes [58], neutrophil dysfunction [59], and HIV/AIDS patients [60], are also at increased risk.

The target population of MRSA infections in the eyes is varied and generally mimics that seen in systemic infections. Reports of MRSA ophthalmic infections are numerous in the literature. They are more commonly seen in patients in neonatal ICUs [61–63], in post-ocular surgical patients [64–75], among healthcare workers [76, 77] after corneal refractive surgery [77–84], in hospitalized pediatric patients [85], and in patients with chronic medical disease, immuno-suppression, or immunodeficiency [70, 86].

Virulence Factors

The success of *S. aureus* as a pathogen is due to a large extent to its ability to resist antimicrobial agents and circumvent the immune surveillance of the host. MGEs play an essential role in this process and are a means to transfer genetic information within species. Many molecular determinants of resistance and virulence are encoded on MGEs. *S. aureus* possesses an enormous repertoire of virulence and persistence genes [20•]. Some of the more commonly studied virulence factors include genome-encoded pore-forming α -toxin [87], PSMs, which are a small group of genome-encoded cytolytic peptides that are key determinants in the development of skin, bloodstream, and biofilm-associated infections [23, 88], and leukotoxins, such as Panton-Valentine Leukocidin (PVL), the effect of which on the pathogenesis of MRSA infection is complicated by its epidemic association with CA-MRSA infections, even though animal and human studies have failed to find PVL as a factor in *S. aureus* virulence. The reader is referred to review articles presenting the molecular basis of *S. aureus* virulence in more detail [23, 89].

Spectrum of Eye Disease

Staphylococcus aureus bacteria are of great interest in ophthalmology, due to their role as a leading pathogen in infections such as conjunctivitis, keratitis, and lid and lacrimal infections. Until recently, studies of ocular MRSA infections have generally been limited to case reports and small case series from single institutions [1, 61–86, 91]. The scant information on ocular infections and the variety of definitions for CA-MRSA [9, 33, 92, 94] makes comparing and contrasting published studies difficult. In addition, many of the earlier studies on MRSA ophthalmic infections do not distinguish CA-MRSA from HA-MRSA entities. Few if any base the distinctions on epidemiologic differences and genomic typing.

Rutar et al. reported on the ophthalmic manifestations of CA-MRSA infections with USA 300 clone in 9 isolates, including orbital cellulitis, endogenous endophthalmitis, and panophthalmitis, and lid abscesses. This was the first report to raise the alarm of aggressive MRSA infections in hospital-naïve patients [91].

Few studies reviewing the epidemiologic, demographic, and microbiologic features of ocular MRSA infections, both HA- and CA-based, in a defined population over a minimum of 5 years exist [2•, 4•, 94]. This may be a result of the fact that most ophthalmic patients are treated in an outpatient setting and treated empirically without culturing based on clinical examination.

Most recently, Amato et al. reported on a retrospective cross-sectional review of all pediatric cases (aged 0–18 years) with culture-positive ophthalmic MRSA in a northern California pediatric population from 2002 to 2009. A total of 137 ocular and periocular pediatric MRSA cases were reviewed. Of the 137 cases, 58 % were community acquired. Conjunctivitis was the predominant presentation (40 %), followed by sty/chalazion (25 %), orbital cellulitis/abscess (19 %), dacryocystitis (11 %), and brow abscess (3 %). The authors reported that pediatric ocular and periocular MRSA was increasing in incidence and resistance in this population [93].

In 2012, Hsiao et al. identified 274 patients with MRSA ocular infections in a 10-year hospital-based study in Taiwan. This included 181 CA-MRSA infections and 93 HA-MRSA infections. They defined CA-MRSA and HA-MRSA infections according to the definition proposed by Naimi et al. and advocated by the CDC [4, 94]. During the study, *S. aureus* was isolated from 519 patients, and 274 (52.85 %) of them were MRSA (181 CA-MRSA and 93 HA-MRSA). The infections included 99 cases of keratitis, 67 cases of lid infections (cellulitis, lid abscess, hordeolum), 28 cases of lacrimal system involvement (caniculitis, dacryocystitis), 10 cases of wound infection, 9 cases of endophthalmitis, and 5 cases of other infections (blebitis, sclera ulcer, scleral buckle infection, and hydroxyappetite implant infection). They found HA-MRSA most commonly caused keratitis (47 of 93 cases), but the rate significantly decreased to 63.5–34.1 % during the last 5 years of the study, while the rate of lid disorders caused by CA-MRSA increased from 17.2 to 37.6 % over the 10-year period. In summary, they reported that approximately two-thirds of ocular MRSA infections were CA and the proportion increased over time. Patients with ocular CA-MRSA infections were younger and had milder disease; they tended to have lid and lacrimal disorders [4].

Blomquist, in 2006, reported an increased prevalence of ocular MRSA infections in an urban public healthcare system from 2000 to 2004 [2]. In this 5-year period, 3,540 patients were identified with culture-positive MRSA infections, with 1,088 (30 %) considered to have acquired the isolate via nosocomial transmission and 2,552 (70 %) considered to have CA-MRSA. Not surprisingly, since the most common manifestations of CA-MRSA are skin and soft tissue infections, his data showed a prevalence of MRSA involving the lids. Forty-nine patients (1.2 %) had ophthalmic MRSA involvement. Twenty-two patients (42 %) had either pre-septal cellulitis, a lid abscess or both, eleven patients had conjunctivitis (21 %; 6 CA-MRSA), five patients (10 %, 2 CA-MRSA) had keratitis, four patients endogenous endophthalmitis (8 %; 4 CA-MRSA), and there were two patients each with blebitis (1CA-MRSA), dacryocystitis (1-CA-MRSA), and orbital

cellulitis with endophthalmitis (4 %). One patient had an orbital abscess (2 %) [2].

Many of the additional reports are laboratory based from records collected from microbiology databases and do not have detailed records of the clinical history or the epidemiologic data. Freidlin et al. reported on 915 positive *S. aureus* cultures over an 18-year period (1998–2006), they found 88 MRSA isolates. The percentage of MRSA isolates increased from 4.1 % in 1998–1999, to 16.7 % in 2005–2006. They had 78 % with blepharoconjunctivitis, 2.4 % with cellulitis, 2.4 % with dacryocystitis, 14.6 % with keratitis, and 2.4 % with endophthalmitis [1]. Lichtinger [95] in an 11 year review of bacterial keratitis in Toronto, found MRSA represented only 1.3 % of the 977 positive corneal scrapings taken over an 11 year period at one institution.

In the last decade, two institutions with dedicated ocular microbiology laboratories have presented their data. Miller et al. examined 484 *S. aureus* isolates recovered during a 6-year period from 2000 to 2005 at the Bascom Palmer Eye Institute (BPEI). Their overall MRSA recovery rate was 29.1 % (141/484). Ocular source rates in descending order were: orbit 33.0 %, conjunctiva 29.3 %, and lids 28.8 %. Of the ocular MRSA isolates, 37 % (53/141) were resistant to 2 or fewer antibiotics. Resistance to the macrolides, clindamycin, and the fluoroquinolones was most commonly seen [3].

Shah et al., from the New York Eye and Ear Infirmary, reported on 16,815 *S. aureus* isolates recovered over a 26-year period [127]. They tabulated their data per decade. From 1984 to 1989, 2,231 isolates were cultured and 155 (6.9 %) were MRSA. From 1990 to 1999, 6,737 *S. aureus* were cultured of which 685 (10.1 %) were MRSA. And, from 2000 to 2009, 7,434 *S. aureus* isolates were cultured of which 966 (13.4 %) were MRSA. In 2010, 415 *S. aureus* isolates were cultured of which 83 (20 %) were MRSA. They noted an increase prevalence of MRSA isolates each decade but no increase in the prevalence of *S. aureus* ulcers over the time period.

In addition to the series above, a comprehensive review of all published MRSA related ocular infection case reports and retrospective small case series is not possible, but Table 1 summarizes the most current MRSA-related case reports and small series in the literature based on infection site and/or specific populations [23, 62–108]. Perhaps the most common are those reported after eye surgery and/or concerning post-operative endophthalmitis. Recent reports in the last decade on endophthalmitis or postoperative infection include small retrospective cases series or case reports following cataract surgery [65, 70, 83, 98], after amniotic membrane transplantation [64], following scleral buckle placement [68], following PK [69], following Ahmed valve placement [71], and after cornea refractive surgery [77–84]. Other reports are frequently site-specific,

including orbital cellulitis [99–104], lacrimal system involvement [91, 105–107], and, most recently, after brow epilation [108].

Ophthalmic Resistance of MRSA

Historically, isolates obtained sporadically and especially from community sources were more likely to be antibiotic susceptible [45]. Continued and occasional inappropriate use of systemic antibiotics has given rise to selective pressure favoring multi-drug-resistant bacterial strains. Such resistance for non- β -lactam antibiotic variably includes aminoglycosides, macrolides, clindamycin, tetracycline, fluoroquinolones, and sulfas among others. MRSA resistance continues to evolve, with expanding resistance to a broad variety of antimicrobial agents. In the hospital setting, it is now becoming a multi-drug-resistant pathogen and showing increasing resistance in CA infections [5, 109, 110•].

Resistance among ocular pathogens is increasing in parallel with the increase among systemic pathogens [110•, 111•, 112]. Data on MRSA antibiotic sensitivity solely from ophthalmic sources has generally been limited to reports from single institutions and retrospective case series [3, 81, 83, 110•, 111•, 112]. However, recent antibiograms from the US and abroad showed that CA-MRSA strains tended to be susceptible to a wide range of non- β -lactam antibiotics [3, 4•, 93, 113].

In the Blomquist report, all ocular CA-MRSA and HA-MRSA isolates were sensitive to trimethoprim/sulfamethoxazole and vancomycin, and more than 80 % of both strains were sensitive to tetracycline and gentamicin [2•]. In the Amato series of pediatric patients, high sensitivities to oral trimethoprim-sulfamethoxazole, gentamicin, and vancomycin were found [93]. This was also seen in the data from Miller et al. [3] at the Bascom Palmer Eye Institute and by Shah et al. [127] at the New York Eye and Ear Infirmary.

Increasing prevalence of MRSA ophthalmic infections has been much ballyhooed in both the peer-reviewed ophthalmology as well as the non-peer-reviewed ophthalmology “throwaways”. Asbell et al. [110•] reported increasing prevalence of multi-drug-resistant MRSA in serious ocular infections based on the rate of increase in a national surveillance program monitoring evolving patterns of antimicrobial susceptibility for pathogens requiring diagnostic testing. The Surveillance Network (TSN) retrieved data from over 580,000 isolates of *S. aureus* from 2000 to 2005 and found methicillin resistance increased in *S. aureus* isolates regardless of specimen source. The MRSA prevalence rate increased 12.1 % during the 5-year period (from 29.5 % in 2000 to 41.6 % in 2005) [114].

Table 1 Methicillin resistant *S. aureus* ophthalmic cases in literature

Larger case series (clinical descriptions/treatment)

Blomquist et al. [2•]

Hsiao et al. [4•]

Amato et al. [93]

Small case series (based on microbiology results or drug trials)

Shanmuganathan et al. [123]

Rutar et al. [91]

Adebayo et al. [124]

Lichtinger et al. [95]

Sotonzono et al. [118]

Case reports site-specific

Lacrimal system

Kotlus et al. [90]

Rutar [107]

Kubal and Garibaldi [105]

Chandravanshi et al. [106]

Gould et al. [125]

Conjunctiva

Tarabishy et al. [85]

Cimolai [61]

Ikeda et al. [119]

Mantadakis et al. [113]

Cellulitis

Mehra et al. [98]

Charalampidou et al. [99]

Juthani et al. [101]

Vaska et al. [104]

Soon [100]

Mathias et al. [102]

Endophthalmitis

Deramo et al. [96]

Major et al. [97]

Ursea et al. [126]

Ho et al. [86]

Basu et al. [62]

Keratitis

Sotonzono et al. [67]

Lee et al. [69]

Chou et al. [65]

Post-surgical case reports

Cataract surgery

Cosar et al. [75]

Tang et al. [70]

Retinal surgery

Oshima et al. [68]

Feiz and Redline [72]

Rich et al. [74]

Pterygium surgery

Lee et al. [73]

Table 1 continued

Glaucoma surgery
Park and Rabowsky [71]
Ocular surface reconstruction
Hori et al. [64]
Cornea cross-linking
Bödemann and Kohnen [66]
Post refractive surgery
Solomon et al. [77]
Woodward and Randelman [78]
Nomi et al. [80]
Magli et al. [79]
Karth and Karth [83]

Published reports of MRSA infections specifically after refractive surgery and cataract surgery at that time raised an ominous specter concerning these infections, especially in light of the fact that many of the cultured organisms had been fluoroquinolone-resistant [75, 77–84]. However, many of the published small reports lack the study power to definitively illustrate the epidemiology of these infections. In addition, ophthalmic culturing practices and geographic location can skew the data and over-represent post-operative infections, infections that respond poorly to initial therapy, and present as severe and potentially sight-threatening infections.

Confounding these MRSA resistance reports is the fact that standard breakpoints for topical antibiotic therapy are not available, and susceptibility data on ocular pathogens is based on the Clinical and Laboratory Standards Institute (CLSI) criteria. These susceptibility/resistance breakpoints are based on drug levels expected in the serum or cerebral spinal fluid after oral or intravenous administration. Although in vitro data are generally accepted as predictive of clinical response, they do not ensure it. Nonetheless, given the high concentration of antibiotics that can be applied directly to the eye, it is generally accepted that antibiotic levels given topically can likely reach or be higher than the CLSI-defined breakpoints for *S. aureus* resistance [110•, 111••]. Hoishi et al. [115], in an in vitro model, were able to demonstrate post-antibiotic effects and increased bactericidal activity against MRSA strains with high- and low-level resistance to levofloxacin and/or gatifloxacin when both antibiotics were given at concentrations simulating topical administration.

Treatment

The majority of antibiotics used to treat MRSA infections target bacterial cell wall synthesis or protein synthesis. Only daptomycin has a novel mode of action [116]. Among the agents currently recommended by the Infectious Disease

Society of America are vancomycin, clindamycin, daptomycin, linezolid, trimethoprim, tetracycline, and the streptogramins (quinupristin/dalfupristin) [117].

A quick perusal of the above medications shows only trimethoprim as an agent available commercially for topical application in the United States. So why are we not seeing a pandemic of ophthalmology infections with MRSA? In my opinion, there may be several answers. First, the MRSA-associated conjunctivitis cases may be self-limiting or controlled with high-dose fluoroquinolone antibiotics topically applied in the United States as first-line therapy. Rarely if ever have I needed to resort to fortified vancomycin to treat chronic MRSA conjunctivitis poorly responsive to therapy. Secondly, many of these infections have been reported in susceptible populations such as hospitalized children or in neonatal units, and these patients may also have concomitant systemic colonization and therefore are treated with appropriate systemic therapy [2•, 21, 85, 117]. Recently, several Japanese authors have reported clinical success in external ocular infections and/or conjunctivitis with minocycline ointment and vancomycin 1 % ointment [118, 119].

In terms of the most severe ocular infections (bacterial keratitis and endophthalmitis), these are commonly treated with intravitreal vancomycin endophthalmitis and fortified topical vancomycin for keratitis. Most of the aforementioned ocular infections in the small case series were treated successfully with traditional endophthalmitis or keratitis protocols, and few if any of the small case reports made alternative treatment suggestions. Our standard regimen for moderate to severe keratitis at the NYEEI is fortified vancomycin and either a later generation fluoroquinolone or an aminoglycoside. Our standard intravitreal protocol also uses vancomycin for Gram-positive organisms and ceftazidime for Gram-negative infections. The lacrimal system infections and orbital infections are treated systemically, and the antibiotic choices can be modified upon culture results.

However, the question is still left unanswered, is our current success short-lived? There are certain strategies that may be useful to decelerate the progress of resistance. These include using culture-directed therapy when possible. If the MRSA is susceptible to an older agent like trimethoprim-polymyxin B, it can be employed. If possible, combination therapy and employing antiseptics like betadine can also play a role.

Although the anti-infective industry has focused on the development of newer generations of conventional antibiotics with improved therapeutic properties, several authors have recently highlighted areas where basic and applied research may offer novel anti-MRSA therapies. Fitzgerald-Hughes et al. [116] discussed cationic antimicrobial peptides and “antipathogenic agents” which interfere with bacterial virulence mechanisms (host binding, biofilm formation, evasion of phagocytosis, and toxin production) as novel therapies to combat MRSA. Cheung et al. [120•] discussed

an immunization therapy that potentially uses multiple antibodies directed against a series of genome-encoded toxins of MRSA. Suzuki discussed antibiotics such as targocil targeting wall teichoic acids (WTA). WTAs are a major polyanionic polymer in the cell walls of *S. aureus* [121]. Koyama et al. [122] discussed several other avenues to target MRSA, including inhibitors of bacterial cell wall peptidoglycan, inhibitors of WTA, and inhibitors of virulence factors such as staphyloxanthin.

Conclusion

Staphylococcus aureus remains a remarkably successful pathogen. It has continued to thrive despite the availability of effective agents to treat it. It continues to be a major cause of morbidity and mortality worldwide. The success of *S. aureus* as a pathogen is due in large extent to its capacity to exist as a commensal, to resist antimicrobial agents, and to circumvent the immune surveillance of its host. MRSA are now well established in both the hospital and community settings. The emergence of CA-MRSA as an important ocular pathogen has occurred in the past 15 years. The ongoing emergence of resistant strains may be readily explained by selective pressure in the healthcare setting. The emergence of antibiotic resistance seen in the systemic literature has now been reported throughout the ophthalmic literature. There still remains a disparity between the prevalence of MRSA among cultured *S. aureus* isolates and the actual percentages of ocular infections caused by the organism. Although MRSA remains the most common cause of skin and soft tissue infections in the USA, the number and percentages of conjunctivitis, lid and lacrimal infections, keratitis, and endophthalmitis infections has not seen similar changes. We are left to wonder, is the epidemic wave of MRSA related ophthalmic infections coming or will the ophthalmic community need to employ new approaches to protect against the high disease burden offered by these organisms?

Disclosure David Ritterband declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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- Of major importance

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