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TOPICS IN Ocular Antiinfectives

Emerging Ocular Pathogens and the Ocular Surface Microbiome

Eduardo Alfonso, MD, and Ying Guo, MBBS, PhD

The rise of methicillin-resistant* Staphylococcus aureus *and other highly resistant organisms will continue to pose challenges to physicians who treat ocular infections. A growing understanding of the normal periocular microflora may yield insight into the mechanisms of pathogenesis and lead to novel antimicrobial therapies.

The past two decades have witnessed a remarkable change in the landscape of ocular infection with, most notably, the rise of multidrug-resistant gram-positive organisms. Among the most worrisome of these newly resistant ocular pathogens is methicillin-resistant *Staphylococcus aureus* (MRSA), which can cause severe infections that can be difficult to diagnose and treat (Figure 1). At one time MRSA infections were confined largely to healthcare facilities, but in recent years they have become prevalent in the larger community.

Although associated with a number of disease states, *S. aureus* can also be a commensal, found on the skin and nasal mucosa of healthy individuals. Increasingly, these commensal staph organisms are MRSA, and this is presumed to increase the risk of MRSA ocular infection.[1]

Recent research has begun to unravel the complex role that surface microbial flora play in ocular health and disease. Beyond simply acting as a reservoir for infection, the organisms normally populating the ocular surface and periocular tissues also function to protect the ocular surface and prevent colonization by more pathogenic organisms.[2] A better understanding of the beneficial role played by the normal surface flora may eventually lead to treatment and preventive measures for infections, including those caused by MRSA.

When to Consider MRSA

Patients with exposure to healthcare environments such as healthcare

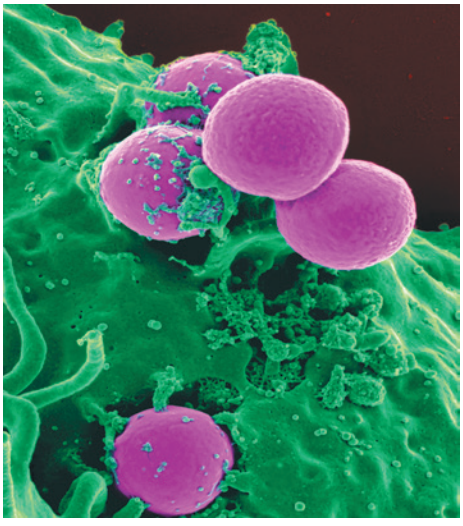

FIGURE 1 Scanning electron micrograph of a human neutrophil ingesting MRSA. *(Image from National Institute of Allergy and Infectious Diseases, National Institutes of Health.)*

See INSIDE for:
The Role of Bacteria in the Pathogenesis of Blepharitis
by Sharmini Balakrishnan, MD, and Stephen C. Pflugfelder, MD

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

LEARNING OBJECTIVES Upon completion of this activity, participants will be able to:

1. Recognize the potential for MRSA infection and select appropriate antibiotics for empirical treatment prior to receipt of culture results.
2. Select appropriate antibiotics for the management of blepharitis.

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workers and nursing home patients are known to have a greater risk of being colonized by resistant organisms such as MRSA. Community-acquired MRSA strains, however, are increasing more rapidly than hospital-acquired strains, suggesting a need for increased vigilance for MRSA carriage even in situations where recognized risk factors such as young age, history of chronic infection, or long-term antibiotic use are absent.

According to Blomquist and coworkers, as many as 76% of MRSA-related ocular infections reported between 2000 and 2004 in a local public healthcare system were caused by community-acquired strains of MRSA, and it is reasonable to believe that this increasing prevalence of community-acquired ophthalmic MRSA is a reflection of national trends.[2,3]

It is not understood yet how *S. aureus* strains circulating in the community become resistant. Among the mechanisms suggested, resistance may be transmitted when healthy individuals happen to capture some resistant organism at hospital settings and become colonized.

Ocular Manifestations

In ophthalmology, we see MRSA infection most often in the form of conjunctivitis.[4,5] Blepharoconjunctivitis cases may account for as much as 78% of all ocular MRSA infections; and, fortunately, blepharoconjunctivitis generally produces mild disease. Ulcerative keratitis caused by MRSA is far more likely to be vision-threatening. However, perhaps the most serious MRSA concerns have to do with postoperative infections following cataract, refractive, and other ocular surgeries. As far back as 2007, it was reported that MRSA infection contributed to about 2.5% of all occurrences of endophthalmitis.[5]

The clinical symptoms of MRSA conjunctivitis and keratitis are essentially the same as they would be if the infecting *S. aureus* were methicillin-sensitive. In general, MRSA ocular infections become apparent only when they fail to respond to typical antibiotic treatment (usually a fourth generation fluoroquinolones or an aminoglycoside); unlike most other treated infections MRSA infections may recur or persist.

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STATEMENT OF NEED

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

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

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

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In the beginning, the patient may improve somewhat with treatment, but when treatment is withdrawn the infection may come back in full force. For this reason conjunctivitis or blepharitis conditions that continue to produce a mucous discharge despite antiinfective treatment—or infections that recur—should create suspicion of MRSA infection; and microbial culture of the ocular surface is called for.

Treatment Challenges

One major challenge clinicians face in battling antibiotic resistance is our limited armamentarium. In vitro susceptibility testing has found that MRSA from ocular isolates are often resistant to not just to methicillin (or methicillin substitutes) but to multiple antibiotics, including the fluoroquinolones.[6,7] The most potent and reliable agent we have for the treatment of MRSA is vancomycin, a glycopeptide antibiotic that inhibits the polymerization of peptidoglycan, an essential component of the bacterial cell wall.

Widespread use of vancomycin, however, has its own issues. Overuse or inappropriate use of antibiotics is known to promote bacterial resistance; and if vancomycin-resistant MRSA were to develop, the loss to global medicine would be massive. In addition, while effective against MRSA, vancomycin is less effective against methicillin-sensitive *S. aureus* than other antibiotics like β-lactam agents—so we cannot simply substitute vancomycin for our fluoroquinlones.[1]

For corneal ulcers, the approach we take in our practice is to start vancomycin early in patients who are MRSA suspects. Our current recommendation is to treat any serious central corneal ulcer empirically with topical vancomycin until the culture and sensitivity results become available.

Since glycopeptides provide only gram-positive coverage, we usually combine vancomycin with a fourth generation fluoroquinolone for broad-spectrum coverage. Once the pathogenic organism is identified, further actions can be taken. In cases of MRSA infection we will simply continue vancomycin treatment and discontinue the fluoroquinolone. If the culture result indicates the infection is not MRSA-related, we can stop vancomycin while continuing the broad-spectrum fluoroquinolone.

Ocular Surface Microflora: Role in Health

Ever since Speaker and coworker's landmark study of endophthalmitis (published in 1991) we have known about the key role ocular surface microbial flora plays in postoperative intraocular infections.[8] Only recently have research findings given evidence that the normal ocular flora may have an opposite—beneficial—role in ocular health: these organisms may preserve ocular surface homeostasis and prevent pathogen invasion.[2]

Normal flora can prevent bacterial overgrowth through several mechanisms: they can produce inhibitory substances, including bacteriocins and other mediators, to limit the number of bacteria in the local environment; alternatively they may simply outcompete pathogens for available nutrients.[9,10] It is believed that the resident microflora population on the ocular surface interacts with the immune cells of the surface epithelia, similar to the situation in the skin and the gut.[2] This interaction between the microflora and their environment may contribute to inflammation inhibition and other ocular surface defenses such as maintenance of epithelial barrier integrity and exclusion of pathogens.

In most cases, problems arise only when the microflora ecosystem is disrupted or when ocular surface integrity has been breached.

Friend and Foe

Analysis of 16S rRNA sequences has allowed profiling of microflora on the healthy ocular surface, and the results demonstrate the great diversity of the normal microbiome.[11-13] A recent study identified more than 220 bacterial species from 59 genera that inhabit the human tarsal conjunctiva.[13] Among these, 12 genera, including *Pseudomonas*, *Staphylococcus*, and *Streptococcus*, were common to all examined subjects and are considered the "core" microbiota of the human conjunctiva.

The composition of the normal ocular flora changes throughout the human lifespan. Today it may contain drug-resistant microorganisms, such as MRSA, which likely exist as passive colonizers rather than active invading pathogens.

If microbes responsible for common ocular infections can thrive as normal components of ocular surface microflora, and, if excluding more pathogenic organisms is one of the most important functions of the surface flora, the question arises: how does the ocular surface distinguish between harmless (or even potentially beneficial) commensal mi-

CORE CONCEPTS

- The prevalence of drug resistance in isolates from ocular infections continues to grow. In particular, MRSA has emerged as a cause of ocular infections including conjunctivitis, keratitis, and endophthalmitis.
- The prevalence of community-acquired MRSA infection is increasing. These strains are also highly resistant to other common antibiotics including the fluoroquinolones.
- Vancomycin is our most reliable agent for use against MRSA, but it is less effective than other agents against the methicilin-susceptible strains.
- Like the skin and intestine, the ocular surface is inhabited by a diverse bacterial community of resident flora.
- The ocular surface flora have opposing roles in ocular surface health. While they are the most frequent source of microorganisms for ocular infections, under normal physiological circumstances they contribute to ocular surface defenses by interacting with the immune system and excluding potential pathogens.

croorganisms and potential pathogens?

The answer is believed to lie in a particular subset of innate immunity receptors that are differentially expressed by cells of the innate immune system residing in the ocular surface epithelium.[14,15] The exact mechanisms by which these receptors mediate the physiological functions of the ocular surface flora and recognize microorganisms are not clear. But there is substantial evidence that one family of such receptors—Toll-like receptors—play an essential role in the pathogenesis of infectious disease on the ocular surface.[15]

Treating the Ocular Surface

While still limited, our knowledge of the roles played by the normal microbial flora to ocular surface health and disease is evolving rapidly. In the near future we may be able to use agents that restore components of the homeostatic ocular surface flora to avoid takeover by pathogenic microorganisms.

Preoperative patients, for example, may benefit from a treatment that maintains the ocular surface microflora and supports its function to prevent certain groups of microorganisms from causing disease. Or a toxin produced by one group of microbes could, perhaps, be used to inhibit the pathogenicity of another. In still another scenario, we may be able to suppress the immune reaction inside the eye to prevent the damaging effects of our reaction to invading microorganisms. (We can do that today with corticosteroids, but these are very broad spectrum in their actions, and not all of their effects are beneficial.) If these developments are at all possible, they may serve as an alternative to the continuous search for new antibiotics for the treatment and prevention of ocular infection.

Eduardo Alfonso, MD, is professor and chairman of Bascom Palmer Eye Institute at the University of Miami Miller School of Medicine in Miami, FL. He states that in the past 12 months, he has not had a financial relationship with any commercial organization that produces, markets, re-sells, or distributes healthcare goods or services consumed by or used on patients. Ying Guo, MBBS, PhD, is a medical writer. She states that in the past 12 months, she has not had a financial relationship with any commercial organization that produces, markets, re-sells, or distributes healthcare goods or services consumed by or used on patients.

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The Role of Bacteria in the Pathogenesis of Blepharitis

Sharmini Balakrishnan, MD, and Stephen C. Pflugfelder, MD

The medical community is just beginning to appreciate the nature and clinical relevance of the body's abundant natural flora, including the many species that inhabit the eyelid and ocular surface. The pathophysiology of blepharitis remains notoriously complex, although fascinating insights surrounding the role of bacteria are emerging.

Inflammation of the eyelids, blepharitis, is one of the most common conditions seen by eyecare practitioners, affecting an estimated 37% to 47% of their patients.[1] Frequently associated with tear dysfunction, blepharitis causes bothersome symptoms of redness, dryness, and ocular surface irritation. Chronic blepharitis can lead to more severe problems, including lid ulceration, lash loss, and corneal ulceration.

Blepharitis is typically categorized according to its anatomical location and what is considered to be the primary etiologic factor. Thus, staphylococcal and sebhorreic blepharitis—which affect the outer lid margin and the eyelashes—are classified as anterior blepharitis; and meibomian gland dysfunction (MGD)—which affects the meibomian glands in the posterior margin of the eyelid—is a form of posterior blepharitis.[2]

In any given case, however, the underlying cause of the blepharitis may not be apparent, and presentations are generally more complex than our categorizations would imply. Blepharitis is increasingly thought to result from highly dynamic interactions between microbiologic, immune, and glandular factors, and may involve both anterior and posterior aspects of the eyelid.[2] Although there is no cure for chronic blepharitis, symptomatic relief may be obtained from treatment with antibiotics, antiinflammatories, and therapies directed at MGD. The range of treatments underscores the disease's complexity and the range of interrelated mechanisms typically involved.

Role of Bacteria

A healthy ocular surface is teeming with an extraordinary diversity of microorganisms: mainly commensals, some environmentally derived and some potentially pathogenic. DNA sequencing studies reveal that core genera include *Staphylococcus*, *Streptococcus*, *Pseudomonas*, *Propionibacterium*, *Corynebacterium*, and *Acinetobacter*; also abundant but lesser known genera including *Brevundimonas*, *Aquabacterium*, *Sphingomonas*, *Streptophyta*, *Bradyrhizobium*, and *Methylobacterium*; as well as dozens of other genera in far smaller numbers.[3]

Resident ocular bacteria may play a significant role in the development and persistence of both anterior and posterior forms of blepharitis.[1] A study by Lee and coworkers revealed a relative abundance of *Staphylococcus*, *Acinetobacter*, and *Corynebacterium* species in the ocular microbiome of blepharitis patients compared to unaffected subjects, suggesting that a higher bacterial load of certain species within the normal eyelid flora might contribute to pathogenesis.[4-6] What we now call staphylococcal blepharitis is probably attributable to the overabundance of more than one bacterial genus; it might be more appropriately termed microbial blepharitis.

The pathogens *Streptophyta* and *Enhydrobacter* spp, are associated with plant pollens, soil particles, and dust; their presence in blepharitis points to a potential role for environmental exposure in blepharitis pathogenesis. Furthermore, a relative paucity of *Bacteroides* and *Propionibacterium* spp among blepharitis patients suggests that certain microbes may play a role in ecosystem maintenance by preventing the proliferation of other species.[5]

Restoring bacterial balance via antibiotics and hygienic measures is often the main thrust of management; the real (albeit often partial) efficacy of these treatments suggests that bacterial population dynamics play some role in blepharitis.

CORE CONCEPTS

- Blepharitis pathogenesis can be inflammatory, bacteriologic, and/or related to meibomian gland function.
- Staphylococcal blepharitis is probably a misnomer, as multiple organisms are likely involved.
- Forms of blepharitis that are not called bacterial likely have a bacterial component.
- Quorum sensing may partially explain how some bacterial populations can become destructive and overtake others in conditions such as blepharitis.
- Bacterial growth can affect meibum composition and vice versa.
- Management of blepharitis should start with assessing possible etiologic factors.
- Therapeutic interventions include eyelid hygiene, antiinflammatory agents, antibiotics, and omega-3 fatty acid supplementation.

Quorum Sensing

Infectious species that are not part of the normal periocular flora, such as the gram-negative bacterium *Moraxella*, cause corneal damage in susceptible individuals via a variety of mechanisms, including the production of endotoxins.[7] But it isn't just invaders from afar that can cause ocular surface disease; harm can come from the bacteria we live with every day: When bacterial species such as coagulase-negative staphylococcus or *S. aureus* grow to sufficient number, they are capable of causing significant damage by generating proteases and lipases that trigger cell-mediated immunity and/or trigger autoimmunity.[6] This begs the question: How do ordinary commensal populations become pathogenic?

An answer may lie in a recently described microbiologic phenomenon called "quorum sensing," the bacterial equivalent of a human "flash mob." Researchers have found that bacteria—just like many animals and humans—are social creatures, behaving differently in groups than they do as individuals. Chemical signaling mechanisms enable some bacteria to count or "sense" their own population density; and when a threshold or "quorum" is reached, a variety of autoinducer genes become activated simultaneously. The products of those genes, which may be secreted or act internally, perform functions designed to benefit the group—anything from nutrient assimilation to toxin production.[8]

Although suspected, a mechanism by which quorum sensing might lead to blepharitis remains to be discovered; however, research is beginning to show how quorum sensing plays a role in diseases characterized by chronic low-grade infection and the presence of biofilms. For example, strains of *Pseudomonas aeruginosa* with intact quorum sensing pathways have been shown to cause microbial keratitis, chronic lung infection, burn wound infection, and other conditions, while mutant strains devoid of such pathways do not.[9-11]

In terms of antimicrobial drug development, the prospect of targeting microbial virulence factors such as quorum sensing (as opposed to targeting viability) could open the door to a more nuanced approach to infectious diseases management, particularly for conditions like blepharitis, which might be better characterized as bacterial population imbalances rather than overt infections. The search for quorum sensing inhibitors derived from a variety of plants—from wheat bran to basil oil—is currently underway.[12,13]

Meibomian Glands and Microbes

The interaction between microbes and the meibomian glands is bidirectional. Bacterial overgrowth on lid margins is thought to exacerbate meibomian gland plugging and perpetuate the cycle of gland dysfunction and ocular discomfort.[1] There is evidence that ocular flora, particularly species that secrete lipolytic enzymes, affect the meibum once it is secreted.[14] *Staphylococcus epidermidis* lipases, for example, break down the wax and sterol esters that stabilize the meibum, resulting in the creation of free fatty acids that can damage the ocular surface.

Some antimicrobial therapies for blepharitis and MGD, including tetracycline, doxycycline, minocycline, and azithromycin, exert at least part of their effect by countering bacterial lipases and restoring the lipid composition of meibomian gland secretions.[15-17] Examining the relationship from the opposite angle, MGD may encourage the growth of microbial pathogens on the ocular surface. And aqueous deficiency associated with MGD reduces the ability of the tears to wash away bacterial toxins; furthermore, altered meibomian gland secretions may promote lipase production among bacteria or select for more aggressive, lipase-producing strains such as coagulase-negative staphylococci and *S. aureus*.[14,18]

Management Points

Management of blepharitis is aimed at suppressing inflammation, reversing bacterial overgrowth on eyelid margins, and relieving ocular symptoms. Eyelid scrubs can be used to remove bacteria or irritating skin oils. Warm compresses, followed by digital massage can express meibum from functional glands. Pharmaceutical therapies include topical antimicrobials, including tetracycline, macrolides, and fluoroquinolones; oral antimicrobials, including doxycycline or azithromycin; and topical antiinflammatory agents, including corticosteroids and cyclosporine.

When considering antimicrobial therapies, it is important to remember that tetracyclines and macrolides possess helpful antiinflammatory and anticollagenolytic properties in addition to their antiinfective properties. Combination antibiotic/corticosteroid agents may increase convenience for patients who require both.[19] Tea tree oil is added to a regimen if Demodex mites are present.

For anterior blepharitis, the practice at our clinic is to initiate lid scrubs and start patients on topical bacitracin or erythromycin applied to eyelid margins once or multiple times daily or at bedtime to be continued for at least 1 week, then as needed for recurrences. For posterior blepharitis, we suggest use of thermomassage if it relieves symptoms and recommend essential fatty acid supplementation. Dietary supplementation with omega-3-fatty acids has been shown to reduce signs and symptoms of inflammation associated with blepharitis and MGD.[20]

Patients who do not respond to initial therapy may be switched to topical azithromycin, which has been shown to improve signs and symptoms or blepharitis and reduce bacterial burden.[21] Low dose oral doxycycline may be used concomitantly for patients who can tolerate it.

Antiinflammatory agents should be chosen with an eye toward long-term safety. Loteprednol etabonate, available alone or in combination with tobramycin, is a rapidly hydrolyzed ester corticosteroid associated with lower risk for raising intraocular pressure compared with other corticosteroids.[19,22] Another option is fluorometholone, a corticosteroid with limited ocular penetration and lower potency. In the treatment of

significant posterior blepharitis associated with MGD, topical cyclosporine may be prescribed. Cyclosporine has been shown to reduce gland plugging, improve tear film quality, and may reduce bacterial overgrowth.[23]

Patients should be followed closely for response to treatment. Neoplasia should be suspected in cases of chronic unilateral eyelid margin inflammation that does not respond to therapy.

Conclusion

Blepharitis is a multifactorial disorder resulting from a combination of inflammatory, bacteriologic, and tear film aberrations. Recently revealed patterns of shifting bacterial populations may be important in the pathogenesis of blepharitis and provide clues to more effective patient care.

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EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 49

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

1. According to the study by Lee and coworkers, which of the following microbial patterns was/were associated with blepharitis?
   A. Higher density of *Staphylococcus* spp.
   B. Lower density of *Propionibacterium* spp.
   C. High rates of fluoroquinolone resistance
   D. A and B

2. The normal ocular surface microflora make NO contribution to:
   A. Infection
   B. Inhibition of inflammation
   C. Corneal oxygenation
   D. Corneal epithelial barrier function

3. MRSA is most susceptible to which of the following antibiotics?
   A. Moxifloxacin
   B. Tobramycin
   C. Vancomycin
   D. Erythromycin

4. Physicians should consider the possibility of MRSA infection in patients with:
   A. A healthcare background
   B. Prior long-term antibiotic use
   C. Recurring or persistent infection
   D. All of the above

5. Which of the following statements is NOT true regarding meibomian gland dysfunction and blepharitis?
   A. They are often concomitant
   B. They are mutually exclusive diagnoses
   C. Both may affect the cornea
   D. Both have been associated with altered bacterial flora

6. Which bacterial genus is NOT commonly found in the normal ocular surface flora?
   A. *Staphylococcus*
   B. *Klebsiella*
   C. *Streptophyta*
   D. *Corynebacterium*

7. Ophthalmic MRSA infection most often takes the form of:
   A. Conjunctivitis
   B. Keratitis
   C. Endophthalmitis
   D. Cellulitis

8. Management of blepharitis is generally aimed at all of the following EXCEPT:
   A. Symptom relief
   B. Inflammation control
   C. Suppression of bacterial overgrowth
   D. Intraocular pressure control

9. Which of the following statements is NOT correct about the resident flora on human conjunctiva?
   A. It is believed to consist of more than 200 bacterial species
   B. It may contain pathogenic microorgansims
   C. Its composition remains essentially fixed throughout life
   D. They interact with the conjunctival epithelium

10. The synchronous activation of genes across the member of a group of bacteria that achieve a certain population density is a product of :
    A. The oxygen response
    B. Cell-cell adhesion
    C. Quorum sensing
    D. Biofilm formation

EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 49

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ANSWERS:

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

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

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    Objective 2: 1 2 3 4 5
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    Related to my practice: 1 2 3 4 5
    Will influence how I practice: 1 2 3 4 5
    Will help me improve patient care: 1 2 3 4 5
    Stimulated my intellectual curiosity: 1 2 3 4 5
    Overall quality of material: 1 2 3 4 5
    Overall met my expectations: 1 2 3 4 5
    Avoided commercial bias/influence: 1 2 3 4 5
13. Will the information presented cause you to make any changes in your practice? Yes No
14. If yes, please describe: _____
15. How committed are you to making these changes? 1 2 3 4 5
16. Are future activities on this topic important to you? Yes No

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

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