ANTI-MICROBIAL SURFACES AND MATERIALS FOR CONTACT LENSES & LENS CASES: THE FUTURE & CHALLENGES

Babu Noushad (M.Optom, FLVPEI, FIACLE)
Department of Optometry, Manipal College of Allied Health Sciences, Manipal University, Manipal

BACKGROUND

Advancements in the contact lens (CL) and lens care technologies during the past few decades have contributed significantly to the safety and efficacy of lens wear, making contact lenses an option for more patients than ever before. In fact, it is estimated that over 125million people worldwide are wearing contact lenses and over 90% of them are using some form of soft contact lenses[1]. In India, the contact lens usage has increased significantly for the last 5 years and is expected to grow at 20% per annum.

However, despite the improvements in contact lens materials and the effectiveness of new lens care solutions, some patients still experience lens related adverse responses. The use of contact lenses is known to increase the microbial load in the eye which can adversely affect the corneal health[2]. The harmful impact can range from a mild ocular redness and irritation to a very severe sight threatening situation like *Acanthamoeba* keratitis[3]. Poor contact lens hygiene and microbial contamination of the lens storage case have been observed to be significant risk factors for contact lens related microbial keratitis[4].

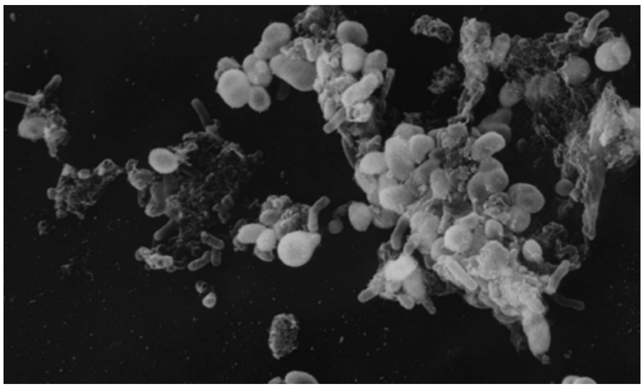
In developed countries, contact lens wear, specifically extended wear with hydrogel lenses, overrides all other risk factors for the development of microbial keratitis in otherwise healthy eyes[2]. The presence of the CL influences development of infection as the lens biomaterial acts as a vector for adherence of microorganisms with subsequent transfer to the ocular surface. Epidemiological studies of contact lens wear over the past 20 years have shown that there remains an almost constant rate of microbial keratitis associated with lens wear; 2-4/10,000 wearers per year if lenses are worn on a daily wear schedule and 20-26/10,000 wearers per year if worn on an extended wear (i.e. sleep in lenses) schedule[5]. Furthermore, contact lens wear is associated with other non-infectious forms of keratitis including contact lens induced acute red eye (CLARE) and contact lens induced peripheral ulcers (CLPU)[6]. Holden et al.[7] have hypothesized that endotoxin released from gram-negative bacteria is a primary cause of the cellular response and infiltration seen when CLs are highly contaminated with gram-negative bacteria. However the pathway between bacterial contamination of CLs and corneal inflammatory events is not as straightforward as the link between CL bioburden and microbial keratitis. There are many other speculative causes of inflammation (lens deposits or defects, hypoxia, cytotoxicity of care solutions, changes in pH and oxygen & CO_2 concentration and corneal surface disruption), which may be present alone or in combination with lens bioburden. Even so, most research has been applied to microbial colonization of CLs as it seems to be the most consistent and repeatable finding and has biologic plausibility.

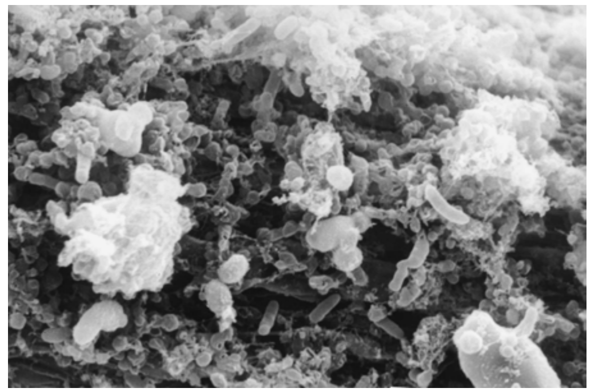
MICROBIAL CONTAMINATION: LENSES Vs CASES

The frequency of storage case contamination is higher than associated lens contamination (fig1). Studies have documented contamination rate as high as 81% on storage cases[8-11]. Assessment of biofilm formed on lenses and lens cases on patients with microbial keratitis revealed that the frequency of contamination and biofilm density was significantly higher on cases than on lens[12]. Unlike lens contamination, which is almost exclusively bacterial, when contamination is detected within solution found in lens cases or on the internal wells, the microorganisms involved are usually mixed contaminants of bacteria, fungi, and protozoa[8-9].

On the other hand, during normal CL wear, the incidence of microbial bioburden on traditional hydrophilic or SiH CLs is approximately 55% to 85%. But, the isolated organisms were majorly bacteria and are mostly considered normal microbiota[13-14]. Although Gram negative and other pathogenic organisms were also present, they are found much more sporadically and in a smaller percentage. This highlights the potency of the ocular defense mechanism. These defense mechanisms include blinking (which mechanically removes loosely adherent organisms); immunoproteins and mucin, which kill or inhibit organisms; and normal ocular flora, which inhibit the growth of pathogens by consuming nutrients and secreting antimicrobial toxins. A common misperception is that microbial bioburden increases gradually on lenses over time. Studies have shown that there is no increase in the colonization of lenses by potential pathogens or normal flora with length of wear or age of lens[15]. However, there are contradicting reports in terms of bioburden on Hydrogel & SiH lens materials[16-17].

(a)





(b)

Fig 1:(a) A biofilm on a contact lens, with clumps of cocci and sparse rods, while the lens case from the same patient (b) has a similar but more extensive biofilm

These findings are giving an insight to the way the user should take care of lens storage cases as its contamination causes the transfer of organisms to the lens surface and ultimately to the ocular surface.

BIOFILMS

In this context, it would be interesting to understand a bit more about biofilms. Biofilm is an aggregate of microorganisms in which cells are stuck to each other or to a surface or to both. These adherent cells are frequently embedded within a self-produced matrix of extracellular polymeric substance ('outer shell' or Glycocalyx). The cells of a microorganism growing in a biofilm are physiologically distinct from planktonic cells of the same organism, which by contrast, are single cells that may float or swim in a liquid medium (Definition from Wikipedia). The outer shell protects pathogens on the inside while continuing to recruit free-floating microorganisms. The cycle continues as the biofilm matrix becomes larger, making this complex network of microorganisms more difficult to kill[18].

We also know that the growth of biofilm formation occurs rapidly over the initial two hours for *S. marcescens* and six hours for *P. aeruginosa*[19]. These become the anchor cells, making it easy for other cells to adhere. At this "infant" stage, the biofilm is easy to eradicate because of its loosely connected network of cells. But, once other cells build upon the anchor cells, adherence between them and the contact lens case or lens surface becomes stronger. The mature biofilm begins to produce a substance that has new properties, making it more antimicrobial resistant than individual planktonic cells.

ANTIMICROBIAL SURFACES FOR LENSES & LENS CASES: IMPORTANCE

There are numerous sources of potentially harmful organisms exist in the realm of contact lenses, including the hands and ocular adnexa of the wearer, lenses, lens cases, and water. Eye care practitioners and their staff spend much time and effort educating patients on proper personal hygiene, lens wear, and lens care practices to avoid contamination with infecting agents. Unfortunately, all of those steps require the patient to actively comply with proper instructions. Thus, prevention of lens and storage case microbial contamination is desirable even for compliant patients who use modern care systems. Preventing bacterial adhesion would limit biofilm formation, which could help prevent infection and inflammation. One potential method for preventing bacterial adhesion is the use of antimicrobial agents, which have been used in the medical field for decades. Antimicrobial agents have been used for a wide range of products including orthopedic implants, urinary catheters, spinal shunts and wound dressings, to name a few. Currently, researchers are exploring the option of using antimicrobial surfaces and materials for contact lenses to further improve their safety.

A wide variety of antimicrobial technologies could potentially be employed for use with a contact lens. Some may be applied to the surface of the lens material, while others may be infused directly into the lens polymer. Regardless of how it is created, the goal of an antimicrobial lens is to reduce or eliminate adverse events caused by infective agents. An ideal "antimicrobial lens" would be, among other things, non-toxic to the human cornea and other tissues, would provide broad-spectrum antimicrobial activity, and would have minimal impact on the normal ocular flora.

POSSIBLE ANTIMICROBIAL TECHNOLOGIES FOR USE IN CONTACT LENSES

Researchers are currently investigating several antimicrobial surface technologies for use in the medical field. However, a limited amount of information is published on the use of these agents applied to contact lenses and lens cases

Silver

Silver is a broad-spectrum antimicrobial agent with low toxicity to human tissue when used at therapeutic levels. It has been used since the 19th century to treat infections, and silver nitrate is still used to prevent neonatal ocular infections. Silver retards the adherence and colonization of microorganisms through its many mechanisms of action, including interference with DNA and RNA to inhibit replication, disruption of the cell membrane, interference with cell respiration, and inactivation and alteration of enzyme conformation. It is unlikely that specific bacterial strains could undergo simultaneous mutations to multiple mechanisms to develop resistance to the broad scope of action of silver. To date, no resistant strains have been encountered clinically. Slow release of silver ions from the impregnated silver when it comes in contact with the solution provides the antibacterial property.

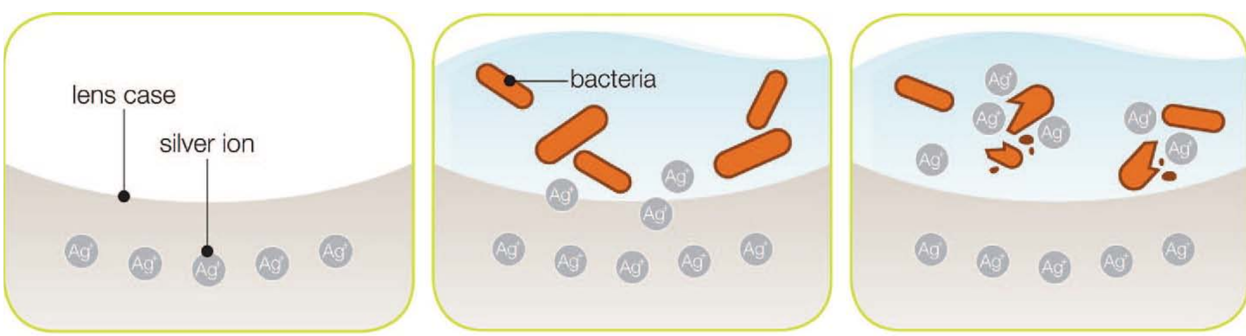


Fig 3: Silver impregnated lens case works by slowly releasing silver ions into the solution to maintain an antibacterial surface.

In vitro studies have shown the efficacy of silver impregnated case against several strains of bacteria, including *Pseudomonas aeruginosa* and a significant 40% reduction in the incidence of bacterial lens case contamination[23]. A very recent study has observed a considerable difference in the antimicrobial capacity of 3 different contact lens cases impregnated with silver[24]. The amount of silver released by each cases as well as its antimicrobial activity against various strains of organisms were also different during the study duration. Further studies are in progress with silver-impregnated cases in conjunction with multipurpose solutions and CLs to better model the in vivo situation. Futhermore, Silver-coated contact lenses have been tested in the laboratory and shown to be effective at reducing the colonization by *Pseudomonas aeruginosa* but not as effective against *Staphylococcus*[25]. Recently, hydrogel lens (etafilcon-A) impregnated with silver nano-particles have shown that silver can prevent colonization of the lens surface by a strain of *P. aeruginosa*, *S. aureus* and *Acanthamoeba*[26].

Antibacterial lens case available in western market: Currently there are 3 types of flat-bottomed cases are available and all are impregnated with silver.

1. MicroBlock Antimicrobial lens case (CIBA Vision, Atlanta, GA): The antimicrobial activity of MicroBlock is achieved by a glass powder additive that releases silver ions in the presence of moisture through ion exchange. The additive is incorporated during the injection moulding process and is present throughout the whole thickness of the plastic. It cannot be worn away and is effective on both the inside and outside of the case.
2. i-clean Antibacterial lens case (Sauflon Pharmaceuticals Ltd., London, UK)
3. Nano-Case (Marietta Vision, Marietta, GA)

Polyquats

Polymeric quaternary ammonium compounds (polyquats) are another option. They are commonly used as disinfectants and preservatives, and algaecides for pools and hot tubs. Polyquats have also been used in contact lens solutions as disinfectants and preservatives. Their efficacy in contact lens solutions is primarily caused by chelation of bacterial components with the compound. More recently, these compounds have been used in dental fillings, catheters, and polymers used in contact lenses to reduce bacterial biofilm formation and adherence to the surfaces of the devices[27].

Polymeric Pyridinium Compounds

Polymeric pyridinium compounds have a broad spectrum of antimicrobial activity and can be covalently bound to surfaces. Upon contact with bacteria, the long amphipathic polycationic chains penetrate the bacterial cell wall. It has been observed that these compounds were active against a broad spectrum of microorganisms and that they did not leach from the surface and thus would not be depleted with time. Researchers have found that they can be applied to contact lens polymers[27].

Free Radical Producing Agents

Free radical-producing agents, such as selenium compounds and nitric oxide-releasing polymers, have been used for antimicrobial coatings as well. Selenium compounds can generate superoxide free radicals which can oxidize bacterial cells and prohibit cell growth. In 2006, Mathews and colleagues published the results of a study investigating silicone hydrogel contact lenses with covalently bonded selenium in a rabbit model[28]. These lenses demonstrated resistance to *P. aeruginosa* colonization *in vitro*. Additionally, after two months of extended wear, corneal health was not adversely affected by the selenium-coated silicone hydrogel contact lenses.

Quorum-Sensing Blockers

Quorum-sensing compounds are another class of agents with potential for use in antimicrobial coatings. The ability of microorganisms to communicate with each other and coordinate behavior is called quorum sensing. Subsequently, Quorum-sensing compounds inhibit bacteria by interfering with their signaling systems. Furanones (one example of quorum sensing compounds) are agents that occur naturally in red algae and prevent bacteria from colonizing on the algae's surface. The antimicrobial effect of adsorbed synthetic furanones on medical device polymers has been studied[29] Baveja and colleagues, have reported that a furanone-coated material significantly reduced *S. epidermidis* bacterial load on the polymer and slime production, while having no significant effect on the substrate's material characteristics. The use of furanones to coat contact lenses has also been studied. In one study, contact lenses were soaked in synthetic furanone, but the study results were unclear[30].

Anti-infective Agents

Anti-infective agents are a different class of agents that kill infectious organisms or prevent them from spreading and causing infection. The human body has potent anti-infectives that naturally occur from neutrophils and macrophages called "Defensins"- small peptides that are rich in cysteine. One family of these naturally-occurring anti-infectives can inhibit bacteria, fungi, and viruses. Defensins bind to the membranes of infecting organisms and increase permeability, decreasing the likelihood of resistance. Lactoferrin is another naturally-occurring anti-infective. It is found throughout the body in mucous membrane secretions, such as saliva, tears, nasal and bronchial secretions, hepatic bile, and pancreatic fluids, and is essential for immune response.

Initial results from Brien Holden Vision Institute[31] are promising and confirm that selenium coated & furanone-coated lenses can prevent bacterial colonization. The overall clinical performance of these lenses in terms of fitting, corneal & conjunctival staining and subjective comfort were comparable to the commercially available lenses.

SUMMARY

Not surprisingly, researchers in the contact lens industry have shown significant interest in agents that would provide antimicrobial properties for surfaces of contact lenses because they could reduce or eliminate the adherence of microbes to contact lenses and lens cases. Reducing exposure to infectious microorganism could make contact lens wear possible for more patients and extended and continuous wear of contact lenses could improve convenience and increase acceptance of contact lenses as a vision care correction of choice. Patients could experience an added measure of protection from microbial contamination without any extra effort on their part. An additional benefit is that bacterial resistance to many antimicrobial agents is unlikely because of their mechanisms of action.

Additional research is needed, and future needs include other aspects of antimicrobial technology, such as whether antimicrobial lenses are compatible with lens care and whether antimicrobial agents could cause an allergic response. It is also unknown whether these agents would have unintended effects such as the build-up of endotoxins. Another concern is the cost of manufacturing antimicrobial lenses. These issues need to be adequately studied, and the answers will aid in the development of contact lenses that incorporate antimicrobial or anti-infective technology.

References

1. Bar JT. 20 years of contact lenses. *Contact lens spectrum* 2006;21:28-38
2. Dart JK, Stapleton F, Minassian D. Contact lenses and other risk factors in microbial keratitis. *Lancet* 1991;338(8768):650-53
3. Stapleton F, Keay L, Jalbert I, Cole N. The epidemiology of contact lens related infiltrates. Optom Vis Sci 2007;84(4):257-72
4. Szczotka-Flynn LB, Pearlman E, Ghannoum M. Microbial contamination of contact lenses, lens care solutions, and their accessories: a literature review. Eye Contact Lens 2010;36(2):116-29
5. *Cheng KH, Leung SL, Hoekman HW, Beekhuis WH, Mulder PG, Geerards AJ, et al.* Incidence of contact-lens associated microbial keratitis and its related morbidity. Lancet.1999;354:181-185.
6. *Jalbert I, Willcox MD.P, Sweeney DF.* Isolation of Staphylococcus aureus from a contact lens at the time of a contact lens-induced peripheral ulcer: case report. Cornea. 2000;19:116-120.
7. Holden BA, La Hood D, Grant T, et al. Gram-negative bacteria can induce contact lens related acute red eye (CLARE) responses. *CLAO J* 1996;22:47-52.
8. Gray TB, Cursons RT, Sherwan JF, et al. *Acanthamoeba*, bacterial, and fungal contamination of contact lens storage cases. *Br J Ophthalmol*1995;79:601- 605
9. Larkin DF, Kilvington S, Easty DL. Contamination of contact lens storage cases by *Acanthamoeba* and bacteria. *Br J Ophthalmol* 1990;74:133-135
10. Yung MS, Boost M, Cho P, et al. Microbial contamination of contact lenses and lens care accessories of soft contact lens wearers (university students) in Hong Kong. *Ophthal Physiol Opt* 2007;27:11-21.
11. Devonshire P, Munro FA, Abernethy C, et al. Microbial contamination of contact lens cases in the west of Scotland. *Br J Ophthalmol* 1993;77:41-45.

12. McLaughlin-Borlace L, Stapleton F, Matheson M, et al. Bacterial biofilm on contact lenses and lens storage cases in wearers with microbial keratitis.*J Appl Microbiol* 1998;84:827- 838
13. Mowrey-McKee MF, Monnat K, Sampson HJ, et al. Microbial contamination of hydrophilic contact lenses. Part I: Quantitation of microbes on patient worn-and-handled lenses. *CLAO J* 1992;18:87-91.
14. Hart DE, Reindel W, Proskin HM, et al. Microbial contamination of hydrophilic contact lenses: Quantitation and identification of microorganisms associated with contact lenses while on the eye. *Optom Vis Sci*1993;70:185-191
15. Willcox MD, Harmis NY, Holden BA. Bacterial populations on high-DK silicone hydrogel contact lenses: Effect of length of wear in asymptomatic patients. *Clin Exp Optom* 2002;85:172-175
16. Henriques MC, Sousa M, Lira M, et al. Adhesion of *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* to silicone-hydrogel contact lenses. *Optom Vis Sci* 2005;82:446-450
17. Choo J, Vuu K, Burnham BK, et al. Bacterial populations on silicone hydrogel and hydrogel contact lenses after swimming in a chlorinated pool. *Optom Vis Sci* 2005;82:134 -137
18. Zegans ME, Shanks RM, O'Toole GA. Bacterial biofilms and ocular infections. Ocul Surf. 2005 Apr;3(2):73-80
19. Szczotka-Flynn LB, Imamura Y, Chandra J, et al. Increased resistance of contact lens-related bacterial biofilms to antimicrobial activity of soft contact lens care solutions. Cornea. 2009 Sep;28(8):918-26
20. Gabriel MM, Mayo MS, May LL, et al. In vitro evaluation of the efficacy of a silver-coated catheter. *Curr Microbiol* 1996;33:1-5.
21. Nablo BJ, Rothrock AR, Schoenfisch MH. Nitric oxide-releasing sol-gels as antibacterial coatings for orthopedic implants. *Biomaterials* 2005;26:917-924
22. Baveja JK, Wilcox MDP, Hume EBH, et al. Furanones as potential anti-bacterial coatings on biomaterials. *Biomaterials* 2004;25:5003-5012.
23. Amos CF, George MD. Clinical and laboratory testing of a silver impregnated lens case. *Contact Lens Anterior Eye* 2006;29:247-255
24. Dantam J, Zhu H, Stapleton F. Biocidal efficacy of silver-impregnated contact lens storage cases In Vitro. IOVS 2011;52(1):51-57

25. Nissen S, Furkert FH. Antimicrobial efficacy of a silver layer on hydrogel lenses. Ophthalmologe. 2000;97:640-643.
26. Wilcox DP, Hume BH, Ajay KV, Robert P. Ability of silver-impregnated contact lenses to control microbial growth and colonization. Publicado na J Optom.2010; 03 :143-8
27. Weisbarth RE, Gabriel MM, George M, et al. Creating antimicrobial surfaces and materials for contact lenses and lens cases. Eye Contact Lens 2007;33(6):426-429
28. Mathews SM, Spallholz JE, Grimson MJ, et al. Prevention of bacterial colonization of contact lenses with covalently attached selenium and effects on the rabbit cornea. *Cornea* 2006;25:806-814
29. Baveja JK, Willcox MDP, Hume EBH, Kumar N, Odell R, Poole-Warren LA. Furanones as potential anti-bacterial coatings on biomaterials. Biomaterials. 2004;25:5003-5012
30. George M, Pierce G, Gabriel MM, Morris C, Ahearn DG. Effects of quorum sensing molecules of *Pseudomonas aeruginosa* on organism growth, elastase B production, and primary adhesion to hydrogel contact lenses. Eye Contact Lens. 2005;31(2):54-61
31. Ozkan J. Early experiences with antibacterial silicone hydrogel contact lenses. http://www.siliconehydrogels.org/in_the_practice/09-dec.asp

ANTI-MICROBIAL SURFACES AND MATERIALS FOR CONTACT LENSES & LENS CASES: THE FUTURE & CHALLENGES – MCQ's

1. What is the percentage of soft contact lens users among the total contact lens wearers?
    a. 60%
    b. 80%
    c. 70%
    d. >90%

2. What is the highest risk factor for microbial keratitis in developed countries?
    a. Ocular trauma
    b. Contact lens wear
    c. Co-existing ocular diseases
    d. Systemic diseases

3. Identify the possible cause/s of contact lens related ocular inflammation
    a. Hypoxia
    b. Presence of bacterial endotoxin
    c. Cytotoxicity of care solutions
    d. All of the above

4. Which one possibly can have the greater density of biofilm during asymptomatic lens wear?
    a. Contact lens surface

b. Surface of CL case

c. Solution bottle

d. All of the above

5. Identify the statement which is TRUE

   a. In a biofilm, microorganisms will not be adhered to each other; but adheres to the lens or CL surface.

   b. The cells of a microorganism growing in a biofilm are physiologically same as planktonic cells of the same organism

   c. Biofilm will have an outer shell which protects the organisms inside

   d. It takes at least 36-48hrs for the formation of biofilm on the new lens or case surface

6. Silver retards the adherence and colonization of microorganisms through

   a. Inhibition of DNA & RNA replication

   b. Disruption of the cell membrane

   c. Interference with cell respiration

   d. All of the above

7. Polymeric quaternary ammonium compounds used in CL solution acts as

   a. Disinfectant

   b. Buffering agents

   c. Viscosity enhancing agents

d. Cleaner

8. Polymeric Pyridinium Compounds
    a. Prevents bacterial multiplication
    b. Penetrates the bacterial cell wall and destroys
    c. Oxidize bacterial cells and prohibits cell growth
    d. None of the above

9. "Defensins" are
    a. Quorum-Sensing blocker
    b. Anti-infective agent
    c. Free-radical producing aent
    d. Polyquat

10. During asymptomatic contact lens wear, the type of organism isolated from the lens surface are mostly
    a. Gram –ve bacteria
    b. Gram +ve bacteria
    c. Fungi
    d. Protozoa