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Recent approaches to combat various infections in eye

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Abstract--The prevalence of various eye related disorder is increasing rapidly among the global population and the microorganism borne ocular infections are emerging as biggest threat to the healthy functioning of eye during the past few years. Conjunctivitis, keratitis, endophthalmitis, blepharitis, uveitis, cellulitis, and ocular herpes are a few of the more common ocular illnesses. The arrival of novel technologies including nanotechnology and ocular implant are giving a hope to the healthcare sector via improved therapeutic potential and safety profile in the field of ocular infections treatment. This article enlisted major ocular infections, along with the physiology, prevention and treatment methods. The review article also highlighted information related to the available treatments for various ocular infections and recent patent insight of emerging technologies.

Keywords--Ocular drug delivery, nanoparticles, liposomes, ocular implants, intraocular, bacterial infections

Introduction

Microorganisms are the main contributor to ocular infections globally. An infection can be single- or multi-microbial in nature, depending on factors such as age, trauma, contact lens use, and a persistently clogged nasolacrimal duct[1-3]. Numerous eye conditions, including conjunctivitis, keratitis, endophthalmitis, blepharitis, orbital cellulitis, and dacryocystitis, are frequently brought on by microorganisms.

The inflammatory reaction known as endophthalmitis (swelling of the interior of the eyes) is brought on by ocular microbial infection and can result in blindness

or visual disturbances[1].The ophthalmic layers that are critical for optical processing, such as the cornea and retina, can be damaged by inner eye inflammation, which is irreversible with standard antimicrobial treatment[2]. After the invasion, the release of fungal endotoxins and proteinases may lead to the secretion on interleukin IL-1 and IL-17 in the eye,which will induce significant inflammation[3–4].

Persistent swelling of the eyes can be caused by the overview of infectious microorganisms either exogenously (as a result of post-traumatic or post-operative conditions) or endogenously (as a result of hematogenous microbial spread from a distantly located infected body part).A severe and long-lasting provocative reaction in the eyes can cause edema, opacity, and finally ocular tissue damage, which can be dangerous. As a result, the inflammation generated by bacterial and fungal infections exacerbates the quality of an affected person's vision. Depending on the harshness of the infection, the inflammatory reaction could cause quick loss of visual insight over numerous days or possibly retinal detachment within 12 hours. As a result, after an infection, the patient should receive fast and effective therapy [4].

By stimulating tissue fibrosis, pathogenic bacteria produce severe tissue swelling, structural disruption, and ocular tissue remodeling [5].After an invasion, the release of proteinases and fungal endotoxins might lead to the secretion of interleukin IL-1 & IL-17 in the eye, which will induce significant inflammation [6].The goal of this review article might be to draw attention to the different difficulties in treating ocular microbial infections. Patents related to treatment of ocular infections are also discussed here.

Methods and Materials

On the basis of the keywords ocular infections, pathophysiology, and treatments of ocular infections, innovative ocular drug delivery systems,and patents related to ocular infections, a literature review was conducted using an electronic database such as Google Scholar,Science Direct,and PubMed.Studies reported until 2022 and focusing on ocular infections were included to obtain concrete findings, highlighting the role of various synthetic drugs and bio actives for the management of ocular infections and patents related to the same were included in the study. Studies published before 1984 were excluded from this review.

Challenges Of Conventional Antimicrobial Treatments for Ocular Microbial Infections

Among the microorganisms that causes eye microbial infections include bacteria, viruses, parasites, and fungi. These microbes have the potential to create infections that are harmful and challenging to treat [7].These germs enter the inner eyes by intraocular surgery, trauma, or metastatic spread from other afflicted anatomical locations, causing a variety of symptoms in patients contingent on the virulence of the microbes and the patient's immunological status as depicted in fig.1. Within a few days of infection, the predominant signs of these contaminations affecting the inner eyes containinjured vision and rapidlyweakening visual insight. During an infection,immune cells and other

substances that are immunologically active will penetrate the intraocular layers, which will then cause inflammatory reactions to occur. Inflammation-induced ocular opacification makes it challenging for the retina to generate a clear image for efficient vision. Furthermore, the fundamental photochemical route for processing light, which includes photoreceptor cells and RPE, is obstructed by inflammation-induced retinal tissue damage. The affected individuals will experience irreparable visual loss as a result of these issues [4].

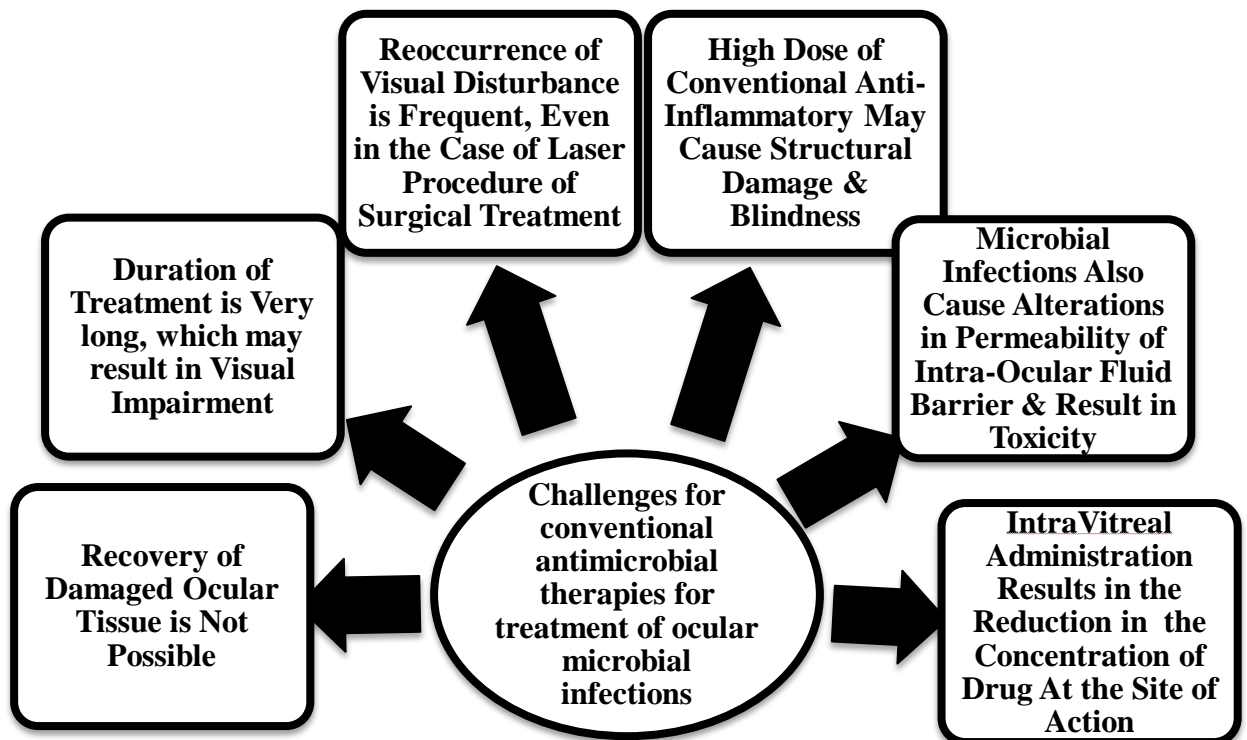


Fig. 1: Challenges for conventional antimicrobial therapies for the treatment of ocular microbial infections [2]

Intraocular Inflammation

As shown in figure 2, there are two different kinds of intraocular inflammation: acute and chronic. Acute inflammation occurs more suddenly than chronic inflammation. Pathogenic bacteria almost usually cause the acute intraocular infection that results from post-operative or post-traumatic endophthalmitis. These infections have the potential to significantly alter the blood-retina barrier's permeability, which may allow non-resident immune cells like macrophages and polymorphonuclear leukocytes (PMNs) to invade. It would seem that a combination of genetic characteristics & environmental triggers accounts for the great majority of cases of persistent intraocular inflammation. Uncontrolled immune tolerance to endogenous antigens frequently leads to the inflammatory eye disease known as uveitis. Autoantibody production, dysregulation of effector and regulatory T cells, and invasion of T macrophages and lymphocytes are the

factors that control this [8]. Autoantibodies are formed when the immune system's tolerance to endogenous antigens breaks down.

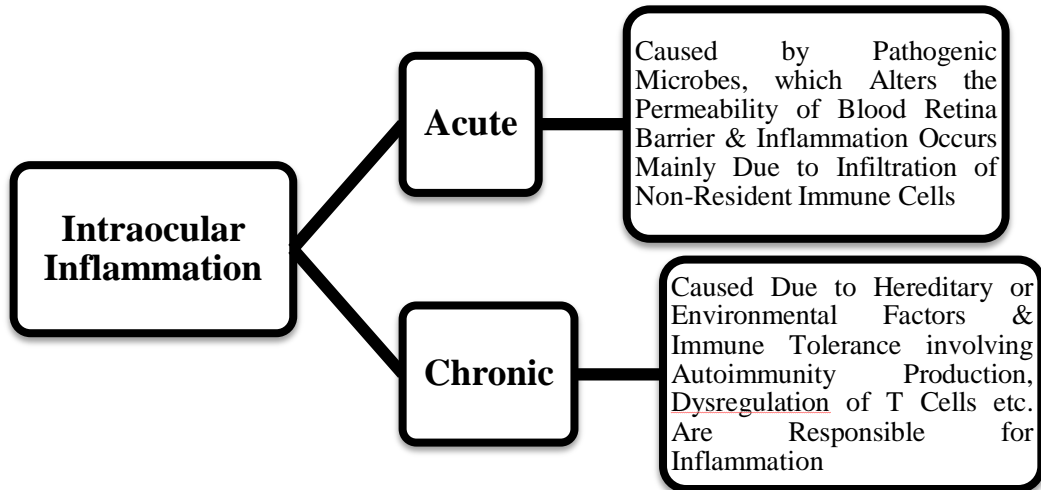


Fig. 2: Types, cause & mechanism of intraocular inflammation

Effect of Age, Sex, Geography/Environment on the Ocular Microbiome

In culture-based studies, variations in the microbiota isolated during life are seen. The neonatal conjunctiva has a broader range of species and more positive cultures just after delivery. Apart from coagulase-negative Staphylococcus & Propionibacterium, the conjunctiva has a microbiota that is comparable to that of the cervix, and after two days, the conjunctiva contains less germs (including dangerous bacteria). Between the ages of 3 and 90, aerobic cocci and Propion bacteria were more prevalent; however, as people aged, Corynebacterium isolation rose and the proportion of anaerobic cocci among anaerobes increased. While other studies found a difference in a normal group, one study (ages 22–64) found no difference in the impact of age on bacterial community structure [9]. Molecular techniques have not yet been used to study the neonatal conjunctiva.

Ocular Viral Diseases

On a worldwide basis, emerging infectious diseases (EIDs) are becoming a greater hazard to public health [10]. All ocular tissues can be impacted by viral infections, which can result in both short-term and long-term vision loss [11]. The bulk of them are herpesvirus-induced ocular infections. The most frequent infectious causes of blindness in the West are HSV-1 keratitis and kerato-uveitis, which result in corneal opacification by reappearances, as shown in fig. 3. The need for long-term antiviral prophylaxis may then arise. 10% to 20% of all instances of shingles are due to herpes zoster ophthalmicus. It is also linked to severe eye involvement (keratitis, kerato-uveitis), and 25% of cases become chronic or keep coming back. Trigeminal neuralgias caused by postherpetic neuralgias can be extremely debilitating. Herpesvirus-induced necrotizing retinitis (HSV, VZV, CMV) is uncommon, but it should be treated as an extreme visual emergency needing immediate intravenous and intravitreal antiviral treatment. The clinical

presentation is influenced by the host's immunological state. Adenovirus is the most common cause of infected conjunctivitis. These infections, which are usually benign, are easily disseminated and can be made worse by corneal lesions that impede vision and can continue for months or years. Inflammatory ocular symptoms have been connected to some arboviruses. For instance, macular or optic atrophy may result from congenital Zika infections. After the acute stage of the Ebola virus infection, conjunctivitis is frequently seen. As a result of the virus staying in the uveal tissues for a long time, up to 15% of survivors develop severe, long-term inflammatory eye problems. Finally, COVID-19-associated conjunctivitis might occur before or after systemic disease, or it can be the disease's sole symptom. Because of viral shedding in tears, extreme caution is required[12].

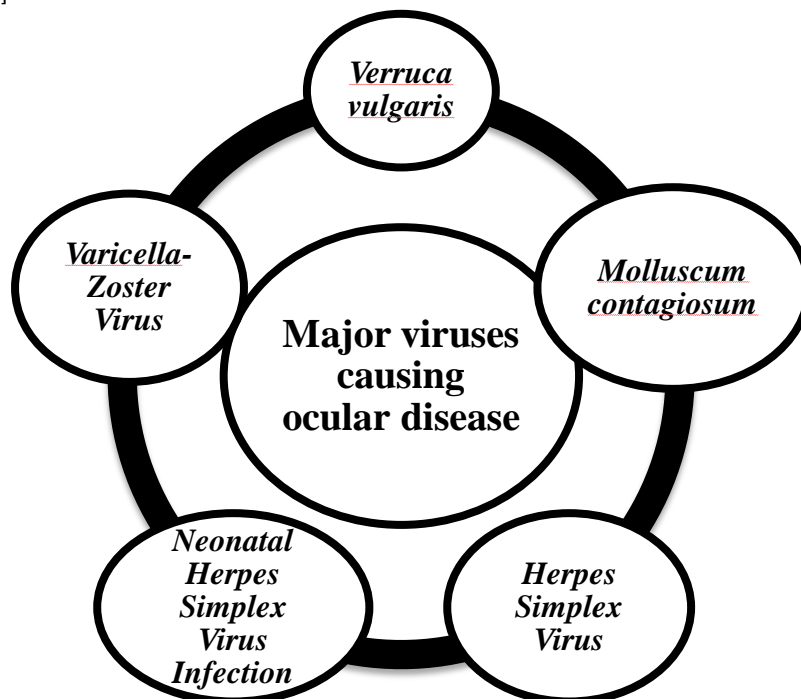


Fig. 3: Major viruses causing ocular disease

Molluscum Contagiosum

The DNA virus Molluscum contagiosum, which is linked to poxviruses, produces a moderate viral infection of the conjunctiva and eyelids [13]. The primary lesion is a dome-shaped, waxy, umbilicated papule that generally appears on the lid border but can occasionally appear on the conjunctiva. The crater is filled with a white, cheesy substance made up of shedding acanthotic epithelium with massive intracytoplasmic inclusion bodies, as determined by histology. Chronic follicular conjunctivitis is caused by the shedding of virally infected cells onto the conjunctiva. The illness is only communicable to a limited extent. As long as there are skin lesions, conjunctivitis remains resistant to treatment. Surgical removal of the papule is the only treatment option [14].

Verruca

Verruca vulgaris is a papillomatous solid lesion that commonly appears on the lid border. A DNA virus from the papova family causes it. The lesion may be asymptomatic or accompanied with a chronic conjunctivitis that is difficult to treat. The treatment of choice is excision [14].

Herpes Simplex

Infection with the herpes simplex virus at its most basic level. Primary herpes simplex virus (HSV) infection occurs in a susceptible host that lacks HSV antibodies. After passively acquired maternal antibodies have decreased or gone, primary HSV arises early in infancy (usually between the ages of 6 months and 5 years). Both the majority of initial infections in children and the majority of cases of herpetic eye illness in all age groups are caused by type 1 HSV. The current treatments for HSV-1 do not completely get rid of the virus from the latent reservoirs or infection sites in the trigeminal ganglia [15]. However, type 2 has only been seen in the eyes of people with ocular illness on a few occasions. HSV infection has a 3 to 12 day incubation period. Fever, pharyngitis, rhinitis, malaise, and lymphadenopathy are common systemic signs and symptoms of the original infection, which is often asymptomatic. Less than 1% of those infected with the virus develop overt ocular illness, according to estimates [14].

Neonatal Herpes Simplex Virus Infection

The ocular signs of HSV infection in newborns commonly appear 2 to 14 days after delivery. In a recent study of 297 neonates with HSV infections, 17 percent of the babies showed ocular damage. Only six cases (2%), on average, had isolated ocular involvement. However, the low number could be due to the difficulties in diagnosing ocular symptoms in the absence of systemic symptoms [14].

Varicella-Zoster Virus

While the varicella-zoster virus (VZV) is the primary cause of varicella (chickenpox), the latent viruses in sensory ganglionic neurons are the primary cause of zoster. Children are most frequently infected with the varicella-zoster virus (VZV), which can be transmitted through contact, droplet, and airborne means. [16] Hope- Simpson found a rate of 0.7 per 1000 per year in infants aged 0 to 9, 1.4 in those aged 10 to 19, and 2.3 to 2.9 in adults aged 20 to 49, with an increasing frequency after 50 [14].

Parasite Ocular Infection & Bacterial Ocular Infection

Different bacteria are continually colonising the cornea & conjunctiva because the ocular surface rapidly reflects light from the outer world. Despite the ocular surface's unbreakable resistance to bacteria, they release pro-inflammatory cytokines that specifically eradicate the local microbiota. One of the major causes of posterior uveitis is ocular infection with *Toxoplasma gondii* [17]. In healthy conjunctiva, gram-negative bacteria like *Haemophilus*, *Neisseria*, & *Pseudomonas* species are rarely isolated. On the other hand, gramme-positive bacteria, such as

Staphylococci, Corynebacterium, Streptococcus, and Propionibacterium species, are regularly identified. Staphylococcus aureus, Streptococcus pneumoniae, & Haemophilus influenzae are some of the microorganisms that have been reported less commonly from the ocular surface as being the source of post-cataract endophthalmitis and keratitis. Due to its finicky development requirements, such a technique could detect extremely common bacteria rather than unusual species. It was eventually defeated by a series of genome-based discoveries, which greatly increased the ocular surface variety [18].

Role of Bacteria in Ocular Infection

A leading factor in loss of vision is bacterial and fungal eye infection [19]. The amount of evidence pointing to bacteria as a major factor in a range of ocular illnesses is staggering all over the world. Infections can be monobacterial or polybacterial, and while they are normally isolated, they can spread to nearby tissues. Dry eyes, obstruction of the nasolacrimal duct, intraocular incursion from other sick regions via the blood stream, bacterial invasion from the outside after ocular surgery or trauma, and microbial colonisation with contact lenses are all associated with these illnesses. Despite having a fully functioning immune system, the ocular surface is the main source of infection since it constantly comes into contact with the outside environment. The most prevalent bacterial eye disorders include conjunctivitis, blepharitis, keratitis, dacryocystitis, orbital cellulitis, endophthalmitis, and panophthalmitis. Ocular adnexal lymphoma could possibly be caused by Helicobacter pylori (OAL) [20].

Conjunctivitis

Allergic conjunctivitis is a rather frequent, underappreciated, and mostly harmless condition [21]. A non-traumatic condition of the conjunctival mucosa known as bacterial conjunctivitis causes irritation, agitation, the discharge of a yellow-white mucopurulent material, and vision loss. There may be detrimental effects from these symptoms. Bacterial infections were shown to be responsible for 50–70% of conjunctival infections, according to studies [18]. Bacterial conjunctivitis is common among people of all ages, including newborns. The bacteria Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Neisseria gonorrhoeae, Haemophilus influenzae, Streptococcus pneumoniae, Aemophilus influenzae, Escherichia coli, Moraxella catarrhalis, Klebsiella spp., & others are one of the primary organisms that contribute.

Keratitis

Infectious keratitis, also known as corneal ulcer, is a dormant sickness of the cornea that can have severe effects on ocular morbidity globally. Infectious keratitis, often known as corneal ulcer, is most frequently caused by bacteria. Herpesviruses are the most common cause of viral keratitis, despite the fact that a number of viruses, including rhabdoviruses, coxsackieviruses, and others, have been discovered as causes of keratitis [23]. A variety of viruses can cause keratitis, an inflammation of the cornea. Keratitis has been associated with Pseudomonas aeruginosa, Streptococcus pneumoniae, Staphylococcus aureus,

Enterobacteriaceae, Nocardia sp., Diphtheroids, Moraxella, & Serratia species. Recent research has shown that Rhizobium radiobacter is one of the primary factors in the development of corneal ulcers [24–28].

Blepharitis

Blepharitis is one of the most exceptional inflammatory illnesses that affects the edge of the eyelids. Some of the most common symptoms of blepharitis include itching, hyperemia, a sensation of a foreign body, burning and coated eyelashes. Blepharitis can be treated with antibiotics. [29] Ophthalmologists assert that blepharitis is the condition that is most usually associated with malfunction in the meibomian glands (MGD). The fundamental blepharitis classifications, which are based on significant symptoms overlap, remain a diagnostic mystery at this time. Disorders like as rosacea, dermatitis, atopy, dry eye diseases, and seborrheic dermatitis are common examples of co-existing or presenting conditions (DES). The progression of blepharitis is thought to be influenced by a wide range of variables, including diet, infections, psychological issues, skin disorders, hormonal imbalances, and other systemic inflammatory illnesses [4,30–31, 38].

Dacryocystitis

Any obstruction in the nasolacrimal duct can result in dacryocystitis, a condition that causes the nasolacrimal sac to enlarge [32]. Stalling tears can cause pathogenic infections or inflammation if the nasolacrimal duct is obstructed. The abrupt onset of pain, redness, swelling over the internal area of the lower eyelid, & epiphora are the defining symptoms of this condition.

Preseptal & Orbital Cellulitis

Erythema & puffiness of the affected eyelid are symptoms of cellulitis, an inflammation of the orbital region. There is damage to the orbital septum. The orbital septum is a membrane that connects the tarsal plates of the eyelid to the margin of the eye socket. It keeps infections from getting into the eye. Bacteria are the most common cause, and it mostly affects children.

Endophthalmitis

Bacteria that enter the front and/or posterior chamber of the eye can cause the uncommon but potentially fatal infection known as bacterial endophthalmitis. Endophthalmitis usually damages the photoreceptor cells in the retina in a way that can't be fixed. This can cause a number of vision problems, including partial or complete loss of vision. Rather than gram-positive bacteria, the most common causes are gram-negative infections caused by Pseudomonas, Klebsiella, Proteus, Haemophilus, and Enterobacter. There are two types of endophthalmitis: exogenous and endogenous.

Pathogenesis of Ocular Microbial Infection

Different bacteria are continually colonising the cornea & conjunctiva because the ocular surface rapidly reflects to the outer world. Despite the impenetrable

resilience of the ocular surface to bacteria, they emit pro-inflammatory cytokines that selectively wipe out the local microbiota. One of the most likely cause of posterior uveitis is toxoplasma gondii ocular infection [17]. Gram-negative bacteria including Haemophilus, Neisseria, and Pseudomonas sp. are rarely isolated in healthy conjunctiva, but Gram-positive bacteria such Staphylococci, Corynebacterium, Streptococcus, and Propionibacterium species are frequently found. Some of the microorganisms that cause post-cataract endophthalmitis and keratitis, which have been reported less frequently from the ocular surface, are Staphylococcus aureus, Streptococcus pneumoniae, and Haemophilus influenzae. Such a technology can detect extremely common bacteria rather than rare species because of its exacting development requirements. A string of genome-based discoveries that significantly enhanced the variety of ocular surfaces ultimately destroyed it [18].

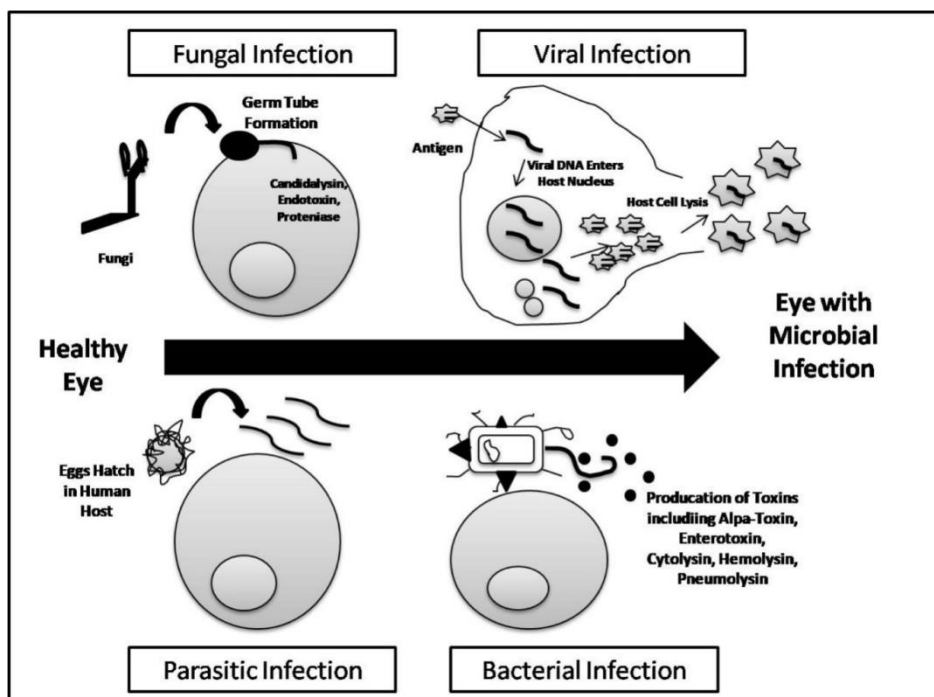


Fig. 4: Pathology of Ocular Infection by Type of Microorganism

Keratitis Infectious

Inflammation of the cornea, often known as a corneal ulcer or keratitis, is the most prevalent cause of this potentially worrisome ocular morbidity globally. The most common cause of corneal ulcers is bacteria. Enterobacteriaceae, Pseudomonas aeruginosa, Nocardia sp., Diphtheroids, Streptococcus pneumoniae, Staphylococcus aureus, Moraxella, and Serratia species have all been linked to the development of keratitis. Rhizobium radiobacter has lately been recognised as a possible contributor to corneal ulcers as one of their potential causes. [33] However, epidemiological forms of infectious keratitis vary by area, with bacterial keratitis being more common in temperate climates than in the tropics. In comparison to other continents, the Indian subcontinent has a low

prevalence of bacterial keratitis. According to a recent analysis of geographic alterations in microbial keratitis, mycological infection accounts for 19–67% of cases in India.[34]

Blepharitis

The most typical symptoms of blepharitis, an inflammatory condition on the edge of the eyelids, include burning, hyperemia, a feeling of a foreign body, and enclosed eyelashes. Ophthalmologists claim that blepharitis and meibomian gland dysfunction are related (MGD). Fundamental categories of blepharitis based on significant symptom overlap, however, remain a diagnostic puzzle. Rosacea, dermatitis, atopy, dry eye syndrome (DES), & seborrheic dermatitis are typical disorders that either accompany or present themselves alongside rosacea. [35] Additionally, a variety of factors, including food, infections, psychological issues, skin disorders, hormonal imbalances, and other systemic inflammatory conditions, have been associated to the growth of blepharitis. These factors have all been found to have a role. Even while bacterial infections are commonly linked to the development of pathogens, the impact of these infections on functioning of the meibomian glands is unknown (MGD). CoNS, *Staphylococcus aureus*, *Corynebacterium macginleyi*, and *Propionibacterium acne* were shown to be contributors to the pathogenic pathway of blepharitis in a study that investigated the microbial ecology of the eyelid edge. [36]

Dacryocystitis

The disorder known as dacryocystitis of the nasolacrimal sac is caused by a bacterial obstruction in the nasolacrimal duct. A blocked nasolacrimal duct will cause pathogenic infection and irritation from stagnant tears. Epiphora, a quick onset of discomfort, redness, & puffiness across the inside area of the lower eyelid, are symptoms of this condition [37]. Acute, chronic, and congenital forms of dacryocystitis are all possible. The main symptom of chronic dacryocystitis is sobbing, and sometimes only one side of the eye cries. This is due to entire or partial blockage of the nasolacrimal duct, which results in chronic dacryocystitis. Gram-positive bacteria like *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Staphylococcus pyogenes*, and *Staphylococcus spp.*, as well as anaerobic bacteria like *Arachniapropionica*, are all involved in the polybacterial illness known as chronic dacryocystitis. However, it was found that gram-negative bacteria like *E. coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and others. *Granulicatella adiacens*, *Chlamydia trachomatis*, and *Mycobacterium tuberculosis* are a few of the microorganisms that can result in chronic dacryocystitis. Females were found to be responsible for 70–83 percent of chronic infections in several comprehensive investigations[39].

Preseptal & Orbital Cellulitis

Erythema & protrusion of the affected eyelid are symptoms of recurrent orbital cellulitis [40]. Erythema & inflammation of the afflicted eyelid also affect the orbital septum are its defining features. The orbital septum, a membrane strip that connects the tarsal plates of the eyelids to the rim of the orbit, serves as a

defence against infection. Its most common cause is bacteria, and it primarily affects children. Preseptal cellulitis is the most prevalent form of orbital inflammation. It affects only the subcutaneous eyelid tissue at the front of the orbital septum and does not result in inflammation within the eye [41]. It can be caused by trauma, an injury, a blister of the lid and periorbital region, or haematogenous seeding. *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* cause preseptal cellulitis [42]. *Acinetobacter*, *Nocardia*, *Bacillus*, *Pseudomonas*, *Neisseria*, *Proteus*, *Pasteurella*, and *Mycobacterium* were additional pathogens linked to preseptal cellulitis. On a few rare occasions, the soil bacteria *Bacillus thuringiensis*, which forms Gram-positive spores, has also been discovered in such contaminations. In contrast, the components behind orbital septum and also eyelids are impacted by orbital cellulitis. It frequently co-occurs with paranasal sinusitis, which is brought on by preseptal cellulitis spreading through the orbital septum or haematogenous seeding. Studies show that the paranasal sinuses are the primary source of ocular cellulitis in 86–98% of cases. *S. pneumoniae*, *S. aureus*, *S. pyogenes*, *H. influenzae* and anaerobic bacteria such as *Fusobacterium* & *Peptostreptococcal* species are the pathogens most frequently associated with orbital cellulitis. Some cases of orbital cellulitis have been linked to bacteria such as *Aeromonas hydrophila*, *Pseudomonas aeruginosa*, and *Eikenella corrodens* [43].

Acute Onset Postoperative Endophthalmitis

The most common cause of this inflammation is cataract surgery, and it often appears six weeks after intraocular surgery. Studies show that post-cataract infection affects 0.03 to 0.2 percent of acute postoperative endophthalmitis. Pars plana vitrectomy, penetrating keratoplasty, scleral buckling, and the placement of glaucoma drainage devices are common causes of acute postoperative endophthalmitis. [34] Acute postoperative endophthalmitis is brought on by preoperative & intraoperative risk factors. Vitreous injury and posterior capsular rupture are intraoperative risk factors. Blepharitis, conjunctivitis, diabetes, and the patient's age are preoperative risk factors. The absence of intracameral antibiotics, corneal wounds, immunocompromised condition, secondary intraocular lens (IOL) types, and leaky surgical wounds are risk factors. The pathogen *CONS* is the most prevalent, followed by *S. aureus* (9.9%) & *Streptococcus* species [34].

Exogenous Endophthalmitis

Exogenous endophthalmitis is caused by the surgical, intravitreal, or traumatic introduction of foreign agents into the eye. When these conditions affect the eye, the permanent & temporary flora of the ocular surface are said to infect the intraocular region. The majority of organisms on the eye's surface are capable of causing irreparable harm to intraocular tissues. Forms of exogenous endophthalmitis are classified according to the infection's cause and the duration of clinical symptoms. [34]

Treatment & Prevention of Ocular Microbial Disease

Ocular rosacea is incurable, despite its severe, possibly lethal effects and

epidemiologic diversity. Treatments have traditionally centered on depressing the severity of symptoms rather than addressing the underlying etiology current research on potential remedies is highlighted, and their efficacy is discussed in fig.5[44,45].

Lifestyle Modification

Multiple harmful compounds, also referred to as "triggers," may exacerbate the alterations brought on by ocular rosacea. Atopic dermatitis may become worse if you consume alcohol, coffee, chocolate, spicy food, hot beverages, or dairy items. Prolonged sun exposure, severe weather, and mental stress can all exacerbate this disease. Astringents, topical irritants, and a number of drugs (such as amiodarone, topical & nasal steroids, and vitamins B6 & B12) can all make symptoms worse[45,46].

As a result, refraining from using these substances is now considered the best way to cure rosacea. Numerous professionals have recommended lipid-free soaps and gentle cleaners. Si-based broad-spectrum sunscreens are commonly used to protect against sun damage. Prevention of potential entities would seem to be a reasonable therapeutic strategy. Still, randomised controlled trials on a large scale have not been done to test how well these treatments work, and patients often find it hard to stick to such a strict lifestyle [47].

Conservative Therapies

Meibomian gland dysfunction caused by ocular rosacea is treated using conservative methods with the goals of preserving gland health, boosting outflow, and calming the ocular surface. To remove dirt & keep gland orifices open, warm compresses and eyelid scraping are frequently utilised. Additionally, digital massage might help the meibomian gland to release its contents. While it is common practise to recommend that patients clean their eyelids with baby shampoo, a few small studies indicate that the number of Demodex colonies, inflammatory symptoms, and visual acuity can be improved by using scrubs containing 50 percent tea tree oil.

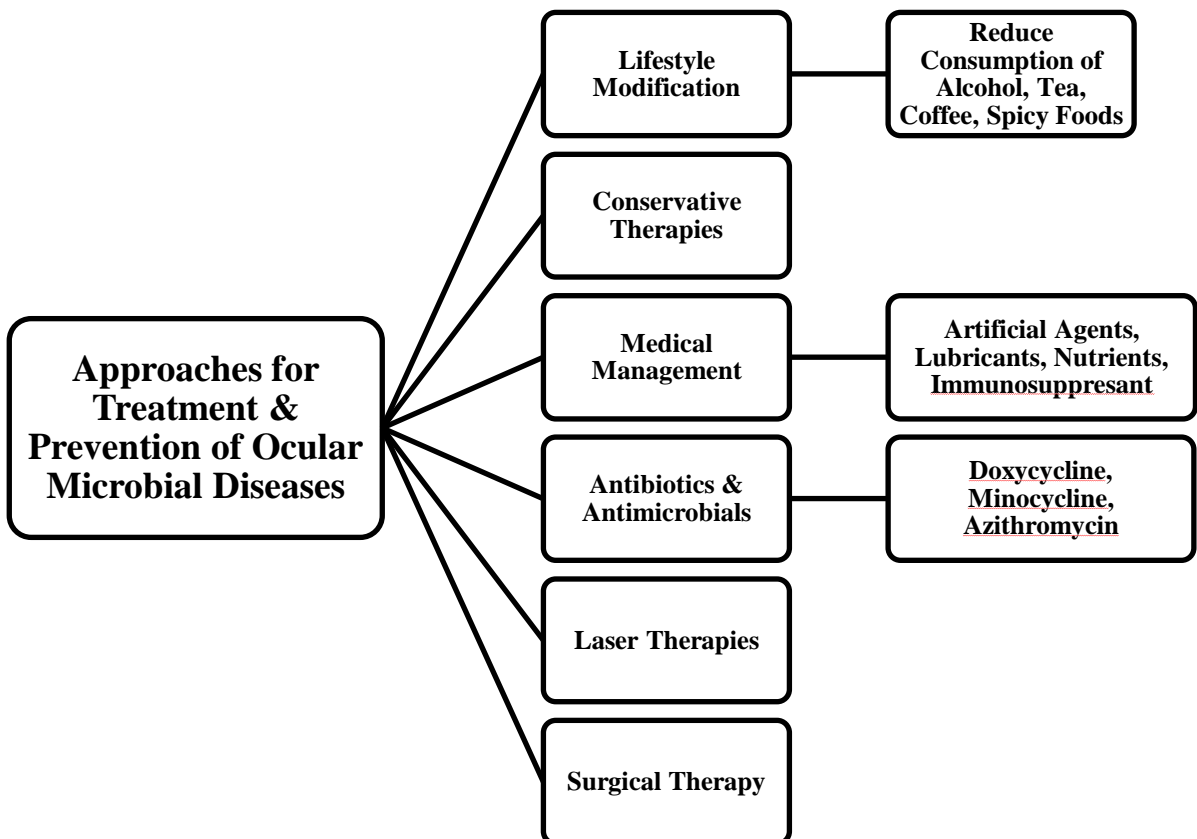


Fig. 5: Approaches for Treatment & Prevention of Ocular Microbial Diseases

Medical Management

There are several, varying degrees of efficacy rosacea treatments available, from topical cream to oral drugs. The management of dry eye disease brought on by meibomian gland dysfunction is one of the main therapeutic objectives for ocular rosacea. Because of this, people have used artificial tears to treat dry eyes caused by skin irritation. Similar to this, using fish oil and flaxseed in your diet may help reduce the symptoms of blepharitis. Oral omega-3 fatty acid therapy alleviated both the subjective symptom and the objective evidence of meibomian gland dysfunction in two meticulously designed studies [46,48]. There are several options for rosacea treatment, ranging from topical ointments to oral drugs with varying degrees of efficacy. Cyclosporine is an immunosuppressive drug that blocks a wide range of T-cell functions. Ophthalmic inflammatory disorders have been successfully treated using topical versions of this drug. Topical cyclosporine instillations twice a day have been displayed to be more effective than artificial tears in treating ocular rosacea's ocular surface modifications and subjective symptoms. In one study, topical cyclosporine surpassed oral doxycycline in terms of symptom relief, eyelid health, and stability and generation of tears.

Antibiotics & Antimicrobials

The effectiveness of oral antibiotics in treating this condition and the inflammation of the meibomian gland has been studied, and there are many indications that they are still being used. These drugs should be viewed as a support for treating ocular rosacea, according to several physicians. The exact methods by which drugs treat ocular rosacea are unknown. Oral antibiotics may have important matrix metalloproteinase properties in addition to being able to kill bacteria.

In addition to their bactericidal qualities, oral antibiotics may also have important characteristics on matrix metalloproteinases, changes in interleukins and nitric oxide, activated B-lymphocytes, and collagen deformities which have been linked to this disorder.

The routine of topical metronidazole enhanced the health of rosacea-related eyelids in a short research. The antibiotics doxycycline, minocycline, and azithromycin have all been thoroughly explored. Although not all investigations indicated arise in acuity or keratitis, and side effects were quite common, numerous researchers have proven improvements in tear break up time and tear production scores, ocular surface signs, and subjective symptoms. Furthermore, due to methodological issues with these trials, a current assessment on the side of the American Academy of Ophthalmology found that the degree of sign was only minor. Oral antibiotics must also be wisely weighed against their likely adverse effects, which comprise photosensitivity, gastrointestinal problems, allergic reactions, teratogenicity, Stevens-Johnson syndrome, and drug interactions[48,49]. Example of some synthetic drugs and herbal drugs available for management of ocular diseases[46-90] are described in Table 1 and Table 2. Patents related to the prevention & treatment of ocular infections & novel ocular drug delivery technologies [91-107] are depicted in Table 3.

Table 1: Example of some synthetic drugs available for the management of ocular Diseases

S.No.	Drug	Treatment	Formulation	References
1	Azithromycin	Ocular surface infections	Ocular Insert	[46]
2	Moxifloxacin	Bacterial conjunctivitis	Nano suspension	[47]
3	Levofloxacin	Conjunctivitis	Ocular Insert	[48]
4	Pefloxacin	Conjunctivitis	Ocular Insert	[49]
5	Neomycin	Eye infections	Hydrogel	[50]
6	Dexamethasone	Inflammation associated with cataract	Suspension	[51]
7	Betamethasone	Eye conjunctivitis	Hydrogel	[52]

8	Posaconazole	Fungal infections	Suspension	[53]
9	Ofloxacin	Bulbar conjunctiva	Topical Hydrogel	[54]
10	Gatifloxacin	Eye infection	Emulsion	[55]
11	Sulfacetamide	Eye infection	Nanosuspension	[56]
12	Cyclosporine	Dry eye syndrome	Microemulsion	[57]
13	Minocycline	Sub-conjunctival infection	Nanoliposomes	[58]
14	Acyclovir	Inflammatory diseases of the sclera	Emulsion	[59]
15	Vancomycin	Eye irritation	In-situ forming gel	[60]
16	Daptomycin	Endophthalmitis	Nanoparticles based formulation	[61]
17	Besifloxacin	Eye infection	Liposomes based topical formulations	[62]
18	Ciprofloxacin	Eye infection	In-situ gels	[63]

Table 2: Example of herbal drugs with active ingredient & bioactivity against ocular diseases

S. No.	Scientific name/common name	Bioactive compound	Bioactivity in ocular disease	Reference
1	Abelmoschus esculentus / Okra	Quercetin	Conjunctivitis	[64]
2	Allium sativum L./ Garlic	Alliin, cysteine, glutathione	Ophthalmopathy, sore eyes	[65,66]
3	Acacia arabica (Lam.) Willd/	Ascorbic acid, Quercetin, Rhamnopyranoside, Oleic acid, Myristic acid, Palmitic acid and steroidal sapogenin	Conjunctivitis	[67, 68]
4	Acer tataricum L./ Tatar Maple	Beta sitosterol, squalene, stigmaterol	Reduce inflammation, dry eye disease	[69, 70]
5	Aegle marmelos L./ Bilvapatra	Marmelosin, phellandrene,	Opacity of cornea, conjunctivitis	[71]

6	Alhagimaurorum / Seez	Actinidiolide, furanacetic acid, terpenoids	Improves eyesight	[72]
7	Azadirachtaindica L. / Neem	Azadirachtin, nimbin, quercetin, nimbidiol	Night blindness, conjunctivitis	[73]
8	Berberis lyceum Royle./ Kasmal	Phytic acid, carotene, anthocyanins	Ocular inflammation, acute conjunctive and chronic ophthalmi	[74]
9	Celosia argentea L./ Guruguaku	Celosin	blurred vision, eye inflammation	[75]
10	Colebrookeaoppositifolia Sm./ Dhurseli	Echioidin, sitosterol, Quercetin	Corneal opacity or conjunctivitis	[76]
11	Daucuscarota Linn./ Carrot	α -pinene, geraniol, myrcene, sabinene	Eye sight, glaucoma	[77]
12	Datura stramonium L./ Datura	Atropine	Iritis, To enlarge pupil in eye	[78]
13	Physostigmavenenosum (Ealf.)/ Ordeal bean	Physostigmine	Glaucoma	[79]
14	Plantago ovata Forssk	Arabinose and Xylose	Eye tumours, eyelid inflammation, conjunctivitis, ophthalmia, cataracts, aching eyes, red, swollen eyes, and retinal inflammation	[80]
15	Ricinuscommunis Linn./ Castor	Ricinoleic acid, stearic, linoleic, palmitic acid, sitosterol, squalene	Blindness, conjunctivitis, related ocular affections, ophthalmic surgery	[81, 82]
16	Plantago ovata Forssk./ Desert Indian wheat	Ascorbic acid Aucubin Tannin	Some of the most common eye disorders are inflammation of the yelid, eye tumours, conjunctivitis, ophthalmia, cataracts, painful eyes, red eyes with swelling, & inflammation of the retina.	[83, 84]
17	Ricinuscommunis Linn./	Stearic acid,	Blindness,	[85, 86]

	Castor	ricinoleic acid, linoleic acid, palmitic acid, sitosterol, squalene tocopherols, and linoleic acid.	conjunctivitis, related ocular affections, ophthalmic surgery	
18	Tamarindus indica L./ Indian Date	β -amyrin, Campesterol, β -Sitosterol	Cataract	[87]
19	Triumfetta rhomboides Jacq./ Bhorachikti		Inflamed eyelids	[88, 89]
20	Vaccinium myrtillus L./ Bilberry	Sineole, α -Pinene, Linalool, α -Terpineol	Vision enhancement, Glaucoma, Cataracts, Diabetic Retinopathy, myopia, & eyestrain	[90]

Table 3: Patents Related to the Prevention & Treatment of Ocular Infections & Novel Ocular Drug Delivery Technologies

S. No.	Title of Patent	Patent Number	Outcome	Reference
1	Topical treatment or prevention of ocular infections	US6569443B1	Topical usage of Azalide antibiotic (Azithromycin) has potential to treat & prevent the ocular bacterial infections	[91]
2	Composition for the treatment of a bacterial infection of the eyes	US6406692B1	Provides information about the ideal composition for the lytic enzyme containing isotonic eye drops for bacterial infection	[92]
3	Natural specific proresolving mediators & their precursors found in anti-inflammatory oils	US10568858B2	Utilizing a Formula, Ocular Inflammation is Reduced including 4-hydroxy-docosahexaenoic acid, 10-hydroxy-docosahexaenoic acid, 17-hydroxy-docosahexaenoic acid, and 18-hydroxy-eicosapentaenoic acid (also known as 18-HEPE) (4-HDHA)	[93]
4	Ocular microcurrent stimulation therapy method and system	US11103705B2	Ocular diseases such as macular degeneration, retinitis pigmentosa, glaucoma, optic	[94]

			neuritis, and other conditions related to the eyes may benefit from microcurrent stimulation therapy.	
5	Compositions and procedures for identifying and treating illnesses of the retina	US20090144839 A1	Method for treating people with risk of developing retinal or choroidal degenerative disease along with the detection and treating AMD and other retinal degenerative conditions	[95]
6	Lipid Nanoparticles for Treating Ocular Diseases	US20130324592 A1	Lipid nanoparticles are able to prevent and treat various Eeye diseases	[96]
7	Using compact nucleic acid nanoparticles to treat ocular illnesses without the use of viruses	US20090011040 A1	The usage of nucleic acid nanoparticles for non-viral gene transfer can several tissues of Human eye.	[97]
8	Utilizing a microneedle, a drug delivery technique for ocular tissue	US7918814B2	Utilizing a microneedle to inject the fluid medication into the corneal stroma or sclera of the eye can increase the effectiveness of drug delivery.	[98]
9	Treatment of posterior segment ocular diseases and conditions with nanoparticles	US10772843B2	The Posterior segment ocular diseases including macular degeneration and diabetic retinopathy can be treated using nanoparticles.	[99]
10	Treatment of vascular abnormalities using nanoparticles	US20080287341 A1	Biocompatible Nanoparticles containing angiogenesis inhibitors drugs can be used for the management of several vascular abnormalities.	[100]
11	Irritation-reducing ocular iontophoresis device	US7548778B2	The Ocular Iontophoresis device is able to reduce the irritation caused during the delivery of various therapies such as nanoparticles, dendrimers, liposomes, emulsions etc.	[101]
12	Photokinetic ocular drug delivery methods and apparatus	US8948863B2	This patent demonstrated how pulsed incoherent light could improve the distribution of biologically active compounds	[102]

			into the scleral, corneal, and transocular spaces.	
13	Sustained release device and method for ocular delivery of adrenergic agents	US20040208910 A1	The Insertable sustained release devices shows improved therapeutic effectiveness in delivering adrenergic agents	[103]
14	Subconjunctival implants for ocular drug delivery	US5476511A	Development of system that can be placed under the conjunctiva for ocular delivery of drug in controlled release manner.	[104]
15	Ocular delivery of polymeric delivery formulations	US20060210604 A1	Provides ideal composition for development of control release implant using biodegradable and biocompatible polymer	[105]
16	Reversible gelling technique for administering drugs to the eyes	US6703039B2	Provides method of delivering the ophthalmic formulation by using gel based system.	[106]
17	Replication competent, a virulent Herpes simplex virus as a vector for neural and ocular gene therapy	US6106826A	involves employing a virulent, replication-competent Herpes simplex virus with ribonuclease reductase deficiency as a vector to replace a defective gene through gene therapy.	[107]

Laser Therapy

Laser treatment for treating ocular rosacea has not received much attention. However, other kinds of illness have also responded well to this medication. Small investigations indicate that the 1064 nm neodymium-doped yttrium aluminium garnet laser and 595 nm pulsed dye laser treatment significantly enhance symptoms, appearance, and quality of life [46].

Surgical therapy

In cases of persistent dry eye disease, punctual occlusion should really be used. Drainage can alleviate frequently recurring chalazion. Due to the possibility of recurrent ulceration, patients may need tissue adhesives, amniotic membrane implantation, or conjunctival coverings, or corneal perforations may require penetrating keratoplasties. Meibomian gland obstructions with extensive scarring may not respond to conservative treatments. Intraductal meibomian gland probing functions by physically opening the cicatrized orifices, allowing the contents to flow and stabilising the tear film. Multiple studies have demonstrated that patients' symptoms improve without major adverse effects. "Lipi flow" is a potential treatment that combines heat and mechanical stimulation of the eyelid

glands to "milk" the glands and encourage the ejection of meibomian gland content [45].

Conclusion

Microbial infections are the most commonly observed complications in the human eye and pathophysiology of these infections makes the treatment very complicated. A novel drug delivery mechanism that can lessen the drawbacks of the currently available treatments and increase their efficacy is urgently needed in addition to the availability of numerous traditional ways for the control of ocular infections. The arrival of nanotechnology opens tons of opportunity in the healthcare sector and researchers of leading organizations consider this approach for development of innovative systems for ocular delivery of drugs. The nano-formulations such as liposomes, microemulsions, nanosuspensions, niosomes and dendrimers etc. are demonstrating beneficial effects in clinical trials and their acceptance is believed to increase in near future.

Along with this, introduction of several other nanotechnology based approaches such as nanoimaging, nanodiagnostics and nonmedicines etc. is also expected to initiate a new era of ophthalmology and it has potential to reduce the probability of critical visual damage and vision loss. Further, the control and sustain release of drugs can also be achieved using insertable ocular implants, which can be an answer for several ocular infections. Certain devices are also believed to get market authorization in near future, which can improve the penetrability of the ocular systems and also able to reduce the possibilities of adverse events. Along with this, gene therapy is also emerging as ideal approach for management of several gene associated ocular diseases and it has potential to prevent the occurrence of ocular infections. Therefore, more accurate and efficient systems for ocular drug delivery are expected to emerge as alternatives for conventional systems and it will transform the ocular infection therapeutic segment.

Authors Contribution

All the authors contributed equally.

Conflict Of Interest

Nil

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