Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-1 Issue-4 || October 2022 || PP. 13-25

https://doi.org/10.55544/jrasb.1.4.3

Microorganisms' Effects and Mechanisms in Ocular Infections: A Systematic Review

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www.jrasb.com || Vol. 1 No. 4 (2022): October Issue

Received: 16-08-2022	**Revised:** 06-09-2022	**Accepted:** 16-09-2022

ABSTRACT

In the world, microorganisms are the main cause of eye illnesses. Common bacterial infections of the eye, if untreated, can damage the eye's structures and lead to blindness and other visual impairments. The eye may get infected from the outside or as a result of bloodstream-borne germs invading the eye. Infectious bacteria can cause eye infections. Blepharitis, conjunctivitis, Listeriosis, keratitis, dacryocystitis, etc. are some of the frequent eye illnesses brought on by bacterial and fungal pathogens. The information on the variety of ocular surface microorganisms has been significantly increased by the series of genome-based methods through 16S rRNA gene-based identification.

According to this research, a sufficient number of bacteria have a substantial part in the pathophysiology of eye illnesses, even though certain bacteria contribute to normal ocular processes. As a result, those with good vision can shed light on the intricacy of the ocular microflora and learn more about some visual requirements in addition to their vital contribution to the regular operation of the eye. Under these conditions, it is crucial to establish a quick, dependable, and affordable procedure that will eventually become a standard diagnostic process. In this literature review, many databases have searched, and the review has been methodically conducted to produce specific results for the hard eye infection disorders.

Keywords- Ocular Infection; Ocular microbiome; Bacterial infectious diseases; Molecular diagnosis.

I. INTRODUCTION

The body's most significant organ is the eye. Ocular (Eye) infections are common, and their severity can range from a minor, self-limiting infection to one that threatens your vision. Different eye structures might be affected by ocular infections (Eye ball). The main cause of eye diseases globally is pathogens. The surface of the eye is always at risk from the elements, including harmful microorganisms. Although numerous kinds of microorganisms are often present in conjunctivitis, eyelids, and tears, bacterial infections of the human eye continue to be a prominent factor that might result in vision impairments [1].

Aside from age, contact lenses, trauma, surgery, dry eyes, chronic nasolacrimal duct blockage, prior ocular infections, and other variables, infection can be mono- or poly-microbial [2-4]. Bacteria, viruses, fungi, and parasites can all be the cause of eye infections. Due to their virulence and the host's decreased resistance from a variety of variables, including poor personal cleanliness, unhealthy living circumstances, poor diet, low socioeconomic level, heredity, physiology, fever, and old age, pathogenic microorganisms can cause illnesses of the eyes [5]. If untreated, ocular infections can harm the structures of the eye, resulting in blindness and visual impairments. Even though the eye is tough and kept clean by a constant flow of antibacterial tears, once inflammation and scarring have taken place, they may be difficult to treat and need to be dealt with right away (Ubani, Udo Ahanna 2009). Numerous species of Gram positive and Gramnegative bacteria have strong defence systems that enable them to avoid immune-compromised patients' defences and cause eye injury. Among Gram positive bacteria, Staphylococcus aureus, Streptococci, Corynebacterium (Non-diphtheriae)

ISSN: 2583-4053

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https://doi.org/10.55544/jrasb.1.4.3

Species, and Bacillus Species have developed an arsenal that may cause tissue injury and an inflammatory reaction. (Astley, R et al.,2019, Krishna, S., Miller, L. S. 2012, Otto, M.2014, Miles, G., Movileanu, L., Bayley, H. 2002, Kobayashi, S. D., DeLeo, F. R. 2013, Kochan, T et al.,2012, Teweldemedhin, M et al.,2012, Benton, A. H., Marquart, M. E. 2018, Bagnoli, F et al.,2011, Barocchi et al.,2006, Nelson, A. L et al.,2007, Hynes, W., Sloan, M. 2016, Fischetti, V. A. 2016, Lancefield, R. C. 1959, Lancefield, R. C. 1962, Eguchi, H. 2013, Callegan, M. C et al.,2017, Ton-That, H., Schneewind, O. 2004). Ocular infections due to Gram negative bacteria like Neisseria gonorrhoeae, Chlamydia trachomatis Pseudomonas aeruginosa, and Bartonella Species are still a challenge to deal with and to escape their devastating eyesight impairment (Costumbrado, J., Ng, D. K., Ghassemzadeh, S. 2020, Acharya, T. 2020, Alarcon, I., Evans, D. J., Fleiszig, S. M. 2009). The purpose of this review study was to assemble established and resent knowledge of the virulence factors of these bacteria, and to depict their mechanisms of ocular invasion and damage.

II. ROLE OF BACTERIA IN OCULAR DISEASE

There is a lot of evidence pointing to bacteria as the primary cause of many eye illnesses. Bacterial infections, whether mono or polymicrobial, are frequently localised but can also spread to nearby tissues. Numerous such illnesses are linked to contact lens contamination, external bacterial invasion following ocular surgery or trauma, dry eyes, nasolacrimal duct blockage, and intraocular incursion from other infectious body parts through blood stream. Despite having a fully developed immune system, the ocular surface is the main source of infection because of its constant interaction with the outside environment. Conjunctivitis, blepharitis, keratitis, dacryocystitis, orbital cellulitis, and panophthalmitis are among the most common bacterial eye diseases.

2.1 Conjunctivitis

A non-traumatic inflammatory illness of the conjunctival mucosa known as bacterial conjunctivitis causes discomfort, irritation, a yellow-white mucopurulent discharge, and visual impairment that can progress to serious problems. According to studies, bacterial infections caused between 50 and 70 percent of instances of conjunctivitis (M. Teweldemedhin et al.,2017). All ages, including newborns, are commonly affected by bacterial conjunctivitis. Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Haemophilus influenzae, Neisseria gonorrhoeae, Chlamydia trachomatis, Escherichia coli, Moraxella catarrhalis, Klebsiella spp., etc. are the primary contributing species (N. Perween, D. Bisht, P. Aggarwal 2019). One particularly deadly condition is primary meningococcal conjunctivitis, which is brought on by the serotype B strain of Neisseria meningitides. It causes acute conjunctivitis, particularly in youngsters, and invasive meningococcal illness (P. Murray, A. Nesdale, M. Balm 2016). Additionally, instances of other species, such as Neisseria cinerea, have been documented. Neonatal neonates can get gonorrhoea by maternal transmission at delivery, which is usually linked to sexually transmitted diseases (STIs) (S. Belga et al., 2019). (N. Anuar, N.S. Idris 2018). However, research indicates that other Neisseria gonorrhoeae strains that are unrelated to STIs can also produce gonococcal conjunctivitis (J. Costumbrado, DK. Ng, S. Ghassemzadeh 2020). Another typical bacterium that is frequently passed from an infected woman to her infant after birth is chlamedia. Acute infection from Chlamydia trachomatis-caused neonatal conjunctivitis is far more common in nature (A. Zikic, H et al.,2018). Pseudomonas, Proteus, and Corynebacterium sp. are three more bacteria that are frequently found in newborn conjunctivitis. Additionally, conjunctivitis occasionally resulted in the recovery of anaerobic bacteria such as Bacteroides fragilis, Prevotella, Porphyromonas, fusobacteria, and bifidobacteria.

2.2 Keratitis

Inflammation of the cornea called Keratitis is characterized by corneal oedema — the clear, dome-shaped tissue on the front of your eye that covers the pupil and iris. keratitis otherwise called corneal ulcer is a latent illness to cornea, especially bacteria is the most frequent etiology lead to potentially devastating ocular morbidity worldwide (J.P. Whitcher, M. Srinivasan, M.P. Upadhyay 2001). The most commons bacteria associated with induction of keratitis include E.coli,Pseudomonas aeruginosa, Streptococcus pneumonia, Staphylococcus aureus, Enterobacteriaceae, Nocardia sp., Diphtheroids, Moraxella, Serratia spp. etc recently detected Rhizobium radiobacter as one of the potential cause of corneal ulcer (S. Marasini, et al.,2016). However, epidemiological patterns of infectious keratitis diverge depending on the region with more risk of bacterial keratitis in temperate climate rather than tropics. Indian subcontinent accounts for low proportion of bacterial keratitis compared with other continents. A recent review on geographical variations in microbial keratitis showed that fungal infection contributes 19–67% in India (A. Shah et al.,2011). Though human eye has natural defence mechanisms against infection, predisposing risk factors cause keratitis which include contact lens wear as most incline factor that is proven up to a frequency 1.9 per 10,000 individuals per year amongst daily wearers (F. Stapleton et al.,2008). By far the serious risk associated upon extended wearing of contact lens compared with daily use accounts to an annual prevalence rate of 20 per 10,000 wearers (J.K. Dart et al.,2008). While considering other factors, difference type of trauma is one of the major predisposing phases that are associated with pediatric microbial keratitis. Also, it is more

ISSN: 2583-4053

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https://doi.org/10.55544/jrasb.1.4.3

associated with additional factors such as systemic conditions and undernourishment that potentially inhibit wound healing process thereby pronouncing the chance of infection (E.B. Koo, K. Colby 2017).

2.3 Endophthalmitis

Endophthalmitis is one of the most devastating ocular infections and may lead to irreversible blindness in the infected eye within few hours or days of symptom onset. The period of "endophthalmitis" refers to infection of the vitreous and/or aqueous by bacteria or fungi. Intraocular infections by pathogens are usually considered types of uveitis rather than endophthalmitis. Endophthalmitis perhaps either exogenous, in which microbes on the ocular surface or from an external source are introduced into the eye, or endogenous. The Supply of pathogens in exogenous endophthalmitis is the ocular Floor (e.g., in postoperative, postinjection, keratitis-related, bleb-related, or device-related endophthalmitis) or the Surronding (e.g., in posttraumatic endophthalmitis).. In endogenous endophthalmitis, the radix of infection is either a transient focus or an ongoing one. The percentage rate of endophthalmitis after cataract surgery is nearly 0.1%, for example, while the rate after penetrating eye trauma is 1-18 percent. Postoperative and posttraumatic endophthalmitis are the major number of types endophthalmitis seen worldwide, with postoperative (primarily post cataract) cases accounting for 40- 80 percent and posttraumatic cases comprising 2 – 15 percent all of endophthalmitis cases seen at centers in India Brazil, England, Israel, Iran, Australia, and South Korea (Melo GB et al.,2011, Gupta A et al.,2014, Falavarjani KG et al.,2012, Moloney TP, Park J 2014, Nam KY et al.,2015, Sharma S et al., 2014, Kessner R, Golan S, Barak A 2014) Regional differences exist: posttraumatic endophthalmitis accounted for 40 to 60% of all endophthalmitis cases treated in some centers in India, China and Egypt (Gharamah AA et al.,2012, Duan F et al.,2016) . The length of time studied has an impact on the occurrence of different forms of endophthalmitis.

The U.S. Food and Drug Administration (FDA) approved intravitreal anti-vascular endothelial growth factor (anti-VEGF) medications to treat neovascular age-related macular degeneration (ARMD) in 2004, and since then, there has been a fast increase in the usage of these and other intravitreal injections. Some centers report that postinjection endophthalmitis is now more common than postoperative endophthalmitis (Simunovic MP.et al.,2012, Kessner R, Golan S, Barak A 2014)

2.4 Ocular listeriosis

Listeriosis is food poisoning caused by eating foods contaminated with the Listeria monocytogenes (L. monocytogenes) bacterium. infection, which typically results in septicemia or meningitis among older adults and immunocompromised persons. Focal infections occur infrequently (Painter J, Slutsker L 2007). Intraocular listeriosis is an exceptionally rare manifestation that typically results in profound vision loss (Betriu C et al.,2001, Eliott D et al.,1992). Since the first published report of a culture-confirmed case in 1967 (Goodner EK, Okumoto M 1967), intraocular listeriosis has been described infrequently in medical literature. With the penetration of listeria into the conjunctiva, the gland-iron form of listeriosis develops. More often older children, less often adults, get sick when they come in contact with infected animals (dogs, cats, rabbits, etc.). Electron microscopy studies are indicating intracellular parasitism of listeriosis in the mucosa of the eyes. This leads to the development of conjunctivitis with mild hyperemia and infiltration, mainly in the upper or lower transitional fold with significant follicular changes. Sometimes among vascularized follicles yellowish granulomas with a diameter of up to 3-5 mm with necrosis in the center are found. Appear mucopurulent discharge, edema of the eyelids, narrowing of the eye gap. A characteristic feature is one-sided defeat. Early diagnosis and treatment of intraocular listeriosis is challenging. Clinical presentation includes pain in eye, high intraocular pressure (IOP), decreased vision, and a fibrinous anterior chamber reaction.

2.5 Dacryocystitis

Dacryocystitis is an infection and inflamation in the nasolacrimal sac resulted by obstruction in the nasolacrimal duct, often caused by bacteria. Such obstacle in the nasolacrimal duct will lead to the stagnation of tear which induce bacterial infection and subsequent inflammation. This can be clinically characterized by rapid onset pain, redness, swelling over the inner portion of the lower eyelid and epiphora (Y. Assefa et al.,2015). Dacryocystitis can happen either in congenital, acute or chronic form (S. Ataullah, B. Sloan 2002). In chronic dacryocystitis, complete or fractional obstruction take place in a single location of nasolacrimal duct with tearing and repeated unilateral discharge as the major symptom (A.G. Janssen et al.,2000). The pathogenecity of chronic dacryocystitis have shown polybacterial infection with predominance of Grampositive bacteria comprising Streptococcus pneumonia, Staphylococcus aureus, Streptococcus pyogenes, Staphylococcus spp and anaerobic bacteria such as Arachnia propionica (J. Hartikainen, O.P. Lehtonen, K.M. Saari 1997, A.C. Delia, G.C. Uuri, K. Battacharjee 2008). However, certain chronic infections revealed the predominance of Gramnegative bacteria such as E. coli, Haemophilus influenzae, P. aeruginosa, Klebsiella pneumoniae etc (M. Chaudhary, A. Bhattarai, S. Adhikari 2010, S. Ahuja, A.K. Chhabra, J. Agarwal 2017). Rarely bacterium such as Chlamydia trachomatis, Mycobacterium tuberculosis and Granulicatella adiacens also has involved in chronic dacryocystitis (B. Janson, S. Idrees 2016, C.A. Ku et al.,2015) Several holistic studies showed that 70–83% of chronic infections were common in females (J. Kandati er al.,2015). Clinicians consider that severe onset of acute dacryocystitis monobacterial infection often predominates with Gram negative

ISSN: 2583-4053

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https://doi.org/10.55544/jrasb.1.4.3

bacteria (Y. Assefa et al.,2015, F. Eslami et al.,2015). However, Gram positive bacteria such as Staphylococcus aureus, Streptococcus pneumonia, Staphylococcus epidermidis, and Micrococcus spp. were also reported commonly in acute infection. Among Gram negative bacteria, P. aeruginosa was the common pathogen followed by Escherichia coli, Klebsiella pneumoniae and Haemophilu influenza were reported (J. Kandati et al.,2015). Unlike chronic infection, severe acute dacryocystitis were more found in male population. However, pathophysiology of dacryocystitis may diverge based on climatic conditions and geographical perspectives. Congenital dacryocystitis is a condition that develops after birth with permanent closure of the Hasner membrane (A. Kuchar, J. Lukas, F.J. Steinkogler 2000). This obstacle predisposes to the postnatal infection and turn out as acute or chronic dacryocystitis.

2.6 Blepharitis

Blepharitis is one of the most frequent inflammatory conditions on the margin of eyelid with predominant symptoms of itching, hyperemia, foreign body sensation, burning and crusted eyelashes (C.M. Putnam 2016). Ophthalmologist reported that blepharatis is most commonly associated with meibomian gland dysfunction (MGD) (E. Knop et al.,2011). However, structural categorizations of blepharitis based on extensive overlapping of symptoms make it to remain as a diagnostic enigma. Often, it coexists or pretense with other disease condition such as seborrheic dermatitis, rosacea, dermatitis, atopy, and dry eye syndrome (DES) (M.A. Lemp, K.K. Nichols 2009). It is also reported that progress of blepharitis depends on other multi factorial conditions such as diet, infections, psychological aspects, skin conditions, hormonal imbalance, and other systemic inflammatory conditions. Considering the pathophysiology, though bacterial infection is well implicated, their effect on meibomian gland dysfunction (MGD) is still unclear. Investigation on microbial flora of eyelid margin found bacteria such as CoNS, Staphylococcus aureus, Corynebacterium macginleyi and Propionibacterium acnes contribute to pathologic route of blepharitis (W.B. Jackson 2008, P. Hossain, A. Konstantopoulos 2015, I.B. Benkaouha et al.,2015). In contrast, sequencing analysis of samples from blepharitis patients suggest that the microbial composition particularly higher concentration of Streptophyta, Corynebacterium, and Enhydrobacter sp. potentially induce chronic blepharitis (S.H. Lee et al.,2012, A. Szkaradkiewicz et al.,2012) reported of infection. Even though direct bacterial infection is not concerned in pathogenecity of MGD, it was reported that their toxins and lipases were pertinent to disruption of eye tissue (J.M. Dougherty, J.P. McCulley 1996, P.J. Driver, M.A. Lemp 1996). Such obstructive MGD would further lead to the incidence of dry eye syndrome (A.J. Bron, J.M. Tiffany 2004). Bacillus oleronius infection in patients with Demodex parasite related chronic blepharitis, where bacteria function as a co pathogen in the development.

2.7 Preseptal and orbital cellulitis

Cellulitis in the orbital area is a common inflammatory condition that affects the orbital septum distinguished by erythema and bulging of the affected eyelid. Orbital septum is a membranous sheet that acts as a barrier to impede infection by extending from the orbital rim and tarsal plates of the eyelid. It is predominantly caused by bacteria and most commonly affects children (J.R. Chandler, D.J. Langenbrunner, E.R. Stevens 1970, E.G. Van der Veer et al.,2017). Among them, preseptal cellulitis is the most common orbital inflammation limited to subcutaneous eyelid tissue anterior to the orbital septum without any intra ocular involvement (T. Ekhlassi, N. Becker 2017). It may be occurred by trauma, an infected wound, an abscess of the lid or periorbital region or through hematogenous seeding (J.J. Kanski, B. Bowling 2012, J.B. Holds 2013). The infectious bacteria involved in preseptal cellulitis comprise Staphylococcus aureus, Streptococcus pneumoniae, and Streptococcus pyogenes (T. Ekhlassi, N. Becker 2017). Other pathogens such as Acinetobacter, Nocardia, Bacillus, Pseudomonas, Neisseria, Proteus, Pasteurella and Mycobacterium were less commonly associated with preseptal cellulitis (B. Crystal, D. Bourget 2018). Bacillus thuringiensis, a Grampositive sporeforming soil bacterium was also rarely reported in such infection (E. Peker et al.,2010). On contrary, Orbital cellulitis affect the structures posterior to the orbital septum and eyelids (S. Fanella, A. Singer, J. Embree 2011). It is commonly associated with paranasal sinuses, which is a direct extension of preseptal cellulitis through the orbital septum or hematogenous seeding (S.P. Donahue, G. Schwartz 1998). Studies reported that 86–98% of orbital celluitis is associated with paranasal sinuses. Most common pathogens associated with orbital cellulitis are S. pneumoniae, S. aureus, S. pyogenes, H. influenzae and anaerobic bacteria such as Fusobacterium and Peptostreptococcal species. In some cases, orbital cellulitis was reported in association with pathogens such as Aeromonas hydrophila, P. aeruginosa, and Eikenella corrodens (A. Danishyar, S.R. Sergent 2018). Rarely, it was also reported Mycobacterium tuberculosis as the cause of orbital cellulitis. Though in adults, orbital cellulitis is through polybacterial infection, rarely single bacterium was also reported among children. In 1970, Chandler classified orbital complications in to five different stages based on severity of the infection to assist with appropriate management (J.R. Chandler, D.J. Langenbrunner, E.R. Stevens 1970).

- Stage I pre-septal cellulitis
- Stage II orbital cellulitis
- Stage III subperiosteal abscess
- Stage IV orbital abscess
- Stage V cavernous sinus thrombosis

ISSN: 2583-4053

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https://doi.org/10.55544/jrasb.1.4.3

Orbital cellulitis may affect other tissues like muscle, bones, and nerves including optic nerve, which lead to a variety of relentless complications including constraint of extraocular movement, central retinal artery occlusion, brain abscess, cavernous sinus thrombosis, intracranial abscess formation, subperiostial abscess, proptosis, cornea opacities, vision loss, meningitis, osteomyelitis and even death have been reported (E.G. Van der Veer et al.,2017,] N.S. Raja, N.N. Singh 2005, W.M. De Melo et al.,2013).

2.8 Panophthalmitis

Panophthalmitis is the inflammation of all cover of the animal eye including intraocular structures. It can be caused by infection, particularly from Pseudomonas species, such as Pseudomonas aeruginosa, Clostridium species.Certain cases of endophthalmitis have a potential to progress in to panophthalmitis, a visually devastating severe condition that affect periocular tissue causing phthisis bulbi, which may require evisceration or enucleation. In most of the cases panophthalmitis is associated with penetrating trauma (R.R. Pappuru et al.,2018). Bacillus cereus, a recurrent ocular pathogen frequently reported in panophthalmitis is often associated with post traumatic or post operative endophthalmitis. However, endogenous B. cereus endophthalmitis is a contradictory entity, which arises as a consequence of hematogenous seeding due to intravenous drug use. Panophthalmitis is also reported with Neisseria meningitis, Mycobacterium tuberculosis, Pseudomonas sp. Clostridia, and Salmonella sp. subsequent to endogenous endophthalmitis (S. Srichatrapimuk et al.,2016). There is a study of endogenous panophthalmitis in a patient with ESBL E. coli urosepsis along with features reminiscent bilateral conjunctivitis. Controversially, bilateral endogenous panophthalmitis was reported in a patient with Streptococcal pneumonia associated meningitis though the same pathogen was not found in ocular infection (L. Krėpštė et al.,2013). Hence it is suggested that frequency of sepsis causing endophthalmitis progressing very rapidly to panophthalmitis.

III. DIAGNOSIS OF OCULAR BACTERIAL PATHOGENS

Microbial culture has been the mainstay of diagnosis of infectious disease since the first pure bacterial cultures were produced by Koch in the 1880**.**An efficient management of ocular infection is a crisis since early diagnosis of pathogens and treatments are the prognostic factors. Systematic microbiological assessments agree to the confirmation of infectious nature, which optimizes medical and surgical treatment so far.

3.1 Conventional microbiological diagnosis

In the past, the only available options for determining the etiologic agents responsible for eye infections were standard microbiological techniques including microscopic inspection and culture of ocular samples (R.K. Forster, R.L. Abbott, H. Gelender 1980, N. Okhravi et al.,1980, G.A. Peyman, D.W. Vastine, H.I. Meisels 1975). In addition to the culture test, microscopic inspection was carried out by making smears for the Gram's and Giemsa staining procedures and creating wet mounts with potassium hydroxide. However, due to a number of factors, including low bacterial inoculums in the specimen that was collected, sequestration of microorganisms on the surface of an intraocular lens or capsule, prior use of antibiotics, a longer time needed to yield growth, and the fastidious growth nature of some bacterial species, conventional techniques still have limitations in terms of sensitivity (P.L. Cornut et al.,2014). Therefore, the majority of suspected eye infections are treated before microbiological tests based on a distinctive look, indirect confirmation of an organism, or the use of a broad range of antibiotics.

3.2 Molecular methods for detecting ocular infections

The early diagnosis and attenuation of ocular infections has showed promise when using molecular biology techniques like PCR. These microorganisms are challenging to find using traditional culture techniques; however, PCR can find them and is compatible with exploring tiny volume samples. Additionally, because to its high sensitivity, minimal microbial inoculum is best suited. The first instance of ocular pathogen identification using PCR for CMV retinitis was documented in 1993. (J. Biswas et al.,1993). In order to examine ocular samples from clinical patients with probable intraocular infections, pan bacterial PCR was adopted after that. In 1994, a polymer chain reaction (PCR)-based 16S ribosomal DNA sequence detection was carried out to determine the presence of bacteria in delayed post-operative endophthalmitis. In order to evaluate samples from patients with postponed post-operative endophthalmitis, nested PCR was used. Global eubacterial primers complementary to sections of 16S rDNA conserved sequences and Propionibacterium acnes specific primers were used (P.G. Hykin et al.,1994). Ocular specimens were subjected to 16S rDNA-based PCR even in situations where the findings of the culture were encouraging (K.L. Therese, A.R. Anand, H.N. Madhavan 1998). Despite the introduction of the 16S rRNA gene PCR, genus and species identification were not done in previous papers. Ocular infections can be caused by a wide variety of possible pathogens, therefore PCR results were further sequenced to pinpoint specific causal organisms. The best method for analysing ocular samples is 16S rRNA gene PCR-based sequencing, which provides more accurate findings with less effort. Direct sequencing cannot identify the polymicrobial community that is typically linked to eye illnesses, which is a major limitation of simple detection of monobacterial identification. Even the Gram reaction of the species involved in each case cannot be provided by it. In order to comprehend the

ISSN: 2583-4053

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https://doi.org/10.55544/jrasb.1.4.3

Gram responses of bacteria in intraocular specimens from patients with infectious endophthalmitis, a novel approach combining PCR and DNA probe hybridization was created (A.R. Anand, H.N. Madhavan, K.L. Therese 2000). Another study employed Gram specific nested PCR to separate 16S rRNA gene sequences from Gram positive and Gram negative bacteria (N.M. Carroll et al.,2000). These experiments have shown how PCR methods may be used to identify the Gram nature of bacteria with greater sensitivity and specificity, even in circumstances when a culture was negative. As a result, Okhravi et al. created PCR-RFLP (restriction fragment length polymorphism) mediated identification of bacterial species implicated in intraocular infections (N. Okhravi et al., 2000). Using the PCR-RFLP approach, it was still difficult to diagnose polybacterial infections. In these situations, denaturing gradient gel electrophoresis (DGGE) and 16S rDNA clone libraries enable profiling of both polymicrobial and monomicrobial populations (Y. Navarro-Noya et al.,2012). Due to their small sequence lengths, infections could not be identified at the species level using this approach. Through the use of amplified PCR products, established a new denaturing High Performance Liquid Chromatography (dHPLC) approach to detect polybacterial infection in endophthalmitis (P. Aarthi et al.,2012). Following this, in 2014 Jayasudha et al. identified endophthalmitis patients using amplifying rRNA gene restriction analysis (ARDRA) approach, which excluded sequencing of sibling strains (R. Jayasudha et al.,2014). Later, similar techniques were used in a study including 36 libraries that discovered the preponderance of polybacterial flora in ocular cases to examine polybacterial diversity in human conjunctiva (S.M. Fleiszig, D.J. Evans 2002). All of these PCR-based methods for diagnosing ocular bacterial infections need postamplification processes, such as gel electrophoresis, probe hybridization, DGGE, RFLP, cloning, ARDRA, and sequencing, which take at least 8 to 10 hours to complete. In contrast, real-time PCR methods are used to diagnose ocular infections with less time and carryover contamination risk. For prompt treatment and the avoidance of future difficulties, a meticulous diagnosis method is especially important for Chlamydia trachomatis, which causes acute conjunctivitis. With a sensitivity and specificity of 95% and 100%, respectively, real-time TaqMan detection (SmartCycler II System) was established by Kowalski et al. for the quick identification of Chlamydia trachomatis from ocular samples (R.P. Kowalski et al.,2006). Similar to this, Goldschmidt et al. created a broad-range real-time PCR technique to find Chlamydia sp. linked to human infections in the eyes and other places (P. Goldschmidt et al., 2006). With 100% specificity and 90% sensitivity, Goldschmidt et al. again introduced fast real-time PCR-based detection of 8 specific genera, including Staphylococcus, Streptococci, Haemophilus, Pseudomonas, Enterobacteria, Acinetobacter, Propionibacteriacae, and Corynebacterial, from endophthalmitis cases in 2009. They created the qPCR process by adding fluorescent probes and primers that are peculiar to certain genera. A broad range quantitative PCR (qPCR) and BLAST analysis were developed by Sugita et al. in 2011 to identify different bacterial species in endophthalmitis infections (S. Sugita et al.,2011). Additionally, multiplex Gram-Specific TaqMan-Based PCR (MGST-PCR) and SYBR Green 16S rDNA-Based Universal PCR (SGRU-PCR) methods were used to detect the Gram reaction of microorganisms linked to endophthalmitis (P.J. Bispo et al.,2011). Sugita et al. created a broad-spectrum real-time PCR of the bacterial 16S rRNA gene with a precise extraction process for identifying infectious endophthalmitis-causing S. aureus, S. epidermidis, S. pyogenes, S. sanguinis, B. cereus, E. coli, and K. pneumoniae (M. Ogawa et al.,2011). For the diagnosis of infections in POE patients in 2012, Joseph et al. used 16S rDNA-based qPCR with Taqman followed by sequencing [167]. The chosen Taqman probe can discriminate between Gram positive and Gram negative bacteria, enabling effective antibiotic treatment right away. Although multiple studies have demonstrated the effectiveness of real-time PCR for certain applications, they were unable to create a single, all-encompassing PCR method that could identify the majority of known diseases from each sample. In order to identify herpes viruses, bacteria, fungi, and toxoplasma in 500 patients with infectious uveitis and endophthalmitis, Sugita et al. combined broad-range bacterial and fungal PCR with multiplex PCR in 2013. (S. Sugita et al.,2013). However, the bacterial species detection test followed the prior findings and used the same broad-range real-time PCR (S. Sugita et al.,2011). To identify ocular Chlamydia trachomatis infections, a next-generation digital PCR diagnostic test was released in 2013. (A. Last et al.,2013). The emulsion PCR method known as droplet digital PCR (ddPCR) provides absolute quantification by splitting nucleic acid material into tens of thousands of nanoliter-sized droplets, each of which performs essentially the same function as a single reaction. This aids in avoiding a number of elements that might harm traditional PCR, such as expense and big sample volume. Kowalski et al. developed a highly sophisticated nucleic acid amplification test (NAAT-GenProbe Aptima Assay) for the identification of Chlamydia trachomatis from ocular samples later in 2015. (R.P. Kowalski et al.,2015).

Target capture, Transcription-Mediated Amplification (TMA), and Hybridization Protection Assay (HPA) technologies are all used by second generation NAAT to amplify target rRNA, identify amplicons, and rationally analyse specimens. Loop-mediated isothermal amplification (LAMP), developed by Notomi et al. for microbial diagnostics, is another promising molecular technique (T. Notomi et al.,2000). This technique amplifies DNA quickly, precisely, and effectively in an isothermal environment without the use

ISSN: 2583-4053

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https://doi.org/10.55544/jrasb.1.4.3

of complicated or expensive equipment. Furthermore, such analysis does not require any post-amplification steps; rather, the outcomes may be quickly and simply seen with the naked eye, free of any carcinogenic substances or UV rays. Recently, a number of researchers used LAMP to identify viral pathogens in ocular diseases (H. Kaneko et al.,2005, A.K. Reddy et al.,2011, J.S. Kumar et al.,2018). LAMP, however, has not yet been successfully used to diagnose bacterial eye infections. Staphylococcus aureus, Streptococcus pneumonia, and P. aeruginosa from eye bacterial infection were not successfully diagnosed using LAMP in our laboratory (Unpublished data). The risk of huge false positives increases in LAMP compared to other molecular approaches, according to a similar discovery made by Senarath et al (K.D. Senarath et al.,2014). The diagnosis of ocular infections has shown great potential because to computational methods and sequencing platforms. In order to detect pathogens from vitreous and aqueous biopsies of endophthalmitis patients, Van Gelder created a novel molecular approach called Biome Representational in Silico Karyotyping (BRiSK) (V. Muthappan et al., 2011). In 2015, Lee et al. investigated BRiSK (A.Y. Lee, L et al.,2015). To identify tags from distinct organisms, the approach uses DNA from biopsy samples by amplifying bp fragments from every 4000 bp of the beginning DNA and comparing them with GenBank database sequences. Analyzing the variety of bacteria on the ocular surface followed a similar process. The ocular surface bacterial populations were then identified by Haung et al. and Jerome et al. utilising the Illumina MiSeq platform and next generation sequencing (NGS) technology. Infectious keratitis is caused by a variety of infections, according to Li et al (Z. Li, F.P. Breitwieser et al.,2018). Formalin-fixed paraffin-embedded (FFPE) specimen from standard surgical pathology examinations were used to produce 20 to 46 million reads per sample utilising next-generation sequencing technology. Deshmukh et al. recently used the Illumina HiSeq technology to sequence the V3-V4 regions of the ITS2 and 16S rRNA genes to identify the microbial diversity in instances of culture-negative endophthalmitis (D. Deshmukh et al.,2019). The study demonstrated that NGS is an effective tool for managing ocular infections with early and accurate pathogen diagnosis as a complement to traditional approaches by identifying opportunistic pathogens such as Acinetobacter spp., Streptococcus spp., Pseudomonas spp., Gemella spp., and Haemophilus spp. in culture negative cases. Sugita et al. combined capillary-type multiplex PCR (S. Sugita et al., 2008) with broad-range quantitative PCR to create a novel multiplex solid-phase strip-based PCR test in 2017. (S. Sugita et al.,2013). In comparison to the prior capillary PCR, which needed expensive equipment and a laborious process, the proposed assay targets 24 ocular pathogens, including bacteria, viruses, fungi, parasites, and amoebae. In order to diagnose bacterial keratitis, the Bacterial Dot Hybridization (BDH) assay was modified by immobilising oligonucleotide probes on nylon membrane to assess the bacterial bioburden of orthokeratology storage cases (M.T. Kuo et al., 2015). This allowed for the detection of Acinetobacter, Klebsiella, and Pseudomonas from suspected patients (P.C. Fang et al.,2017). After grayscale image processing, signals were normalised for objective validation using receiver operating characteristic (ROC) curves. This technique can enable quick examination of Pseudomonas keratitis and provide an approximation of the Pseudomonas load in the diseased cornea (6 h). The MALDI-TOF mass spectrometry (MS) technology was also disclosed by Mailhac et al. in the same year for the quick detection and identification of bacteria that cause endophthalmitis (A. Mailhac et al.,2017). In comparison to conventional identification approaches, the suggested procedure may be evaluated with the supernatant of positive blood cultures towards bacterial detection within 24 hours. Similar to this, another team created a microchip-based method for P. aeruginosa and S. aureus identification from patients with keratitis by on-chip electrical sensing of bacterial lysate (H.J. Pandya et al.,2017). In order to modify the electrical properties of the microbes, streptavidin-coated magnetic beads coupled with biotinylated antibodies were first used to collect and isolate the microbes. Then, using a magnetic standoff-chip, magnetic beads were separated from the lysate, and bacteria were found utilising onchip electrical sensing. An impedance metre was then used to gauge the bacterial lysate samples' impedance changes. Although many molecular approaches have been created, it is still necessary to conduct promising investigations to examine their clinical effect and usefulness in aiding rapid and accurate diagnosis in order to enhance visual outcomes.

IV. MEDICAL TREATMENT OF BACTERIAL INFECTION

Bacterial Eye Infection Treatment for eye infection caused by bacteria are widely available. Medical Treatments Include: Prescription antibiotic eye drops such as Ciprofloxin, Moxifloxin. Tobramycine, Getofloxin etc. Prescription different types antibiotic ointments and Oral antibiotics.

V. HOW TO PREVENT BACTERIAL OCULAR INFECTIONS

A bacterial eye infection happens when noxious microorganisms get within the thin, wet membrane covering the outer and inner eyelids as well as the cornea, the clear front surface of the eye (the conjunctiva). Maintaining awareness and enhancing cleanliness are the first steps in preventing the spread of any of the ailments mentioned above. These advices might be useful:

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Avoid Contact – Avoid making eye contact with somebody who may have pink eye. Don't touch an infected person's excretions since it can be transferred through direct contact.

Wash Your Hands – Wash your hands frequently whether or not you come into close touch. By doing this, you will reduce the possibility that bacteria will get on your eyes, eyelids, or contact lenses. When in public, day care facilities, and schools, use anti-infective sprays and cleansers. If a family member gets an eye infection caused by germs.

Wash Everything They Touch – Family members should not share anything with the sick individual, and all linens, towels, clothing, and other items touched by them need to be washed.

Teach – Children should be taught how to spot an infection in others, what to do if they think someone else may be ill, and how to avoid touching their eyes.

For Contact Lens Wearers – Before handling your contacts, wash your hands. Even if your contact lenses are breathable and FDA-approved for nighttime usage, avoid sleeping while wearing them. As directed, you should also always clean, store, and replace your contact lenses.

VI. CONCLUSION

As sequencing technology developed, it was found that the bacterial community in the human eye was large and diversified. Even though the eye has several components that work to protect it from microbial diseases, a large amount of microbiota competes with them on the ocular surface. Staphylococcus, Streptococcus, Pseudomonas, Corynebacterium, and Propionibacterium are the main taxa found on the ocular surface. By defending the ocular surface microbiota from pathogenic colonisation, it can act as a commensal. There is strong evidence to support the idea that the ocular surface microbiota actively contributes to the pathogenesis of numerous eye disorders.

Additionally, hematogenous seeding can have a significant impact on the pathophysiology of some ocular disorders caused by viral diseases linked to other body areas. Because the microbiology of the eye varies significantly over time, it is necessary to regularly check the ocular micro flora in order to forecast certain infections. Otherwise, such infections cause terrible visual problems that might result in blindness. Therefore, the management of ocular infections requires the development of efficient and trustworthy molecular diagnostic methods. Such diagnostic techniques are necessary for the ongoing study of ocular pathogen dynamics and the recommendation of appropriate medicines for the prevention and treatment of disorders that endanger eyesight.

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