

Ocular Infections Caused by Viruses

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Ocular viral infections are common and widespread globally. These infectious diseases are a major cause of acute red eyes and vision loss. The eye and its nearby tissues can be infected by several viral agents, causing infections with a short course and limited ocular implications or a long clinical progression and serious consequences for the function and structure of the ocular region. Several surveillance studies underline the increased emergence of drug resistance among pathogenic viral strains, limiting treatment options for these infections. Currently, in the event of resistant infections, topical or systemic corticosteroids are useful in the management of associated immune reactions in the eye, which contribute to ocular dysfunction.

antiviral drug

corticosteroids

viral infection

viruses

1. Introduction

The eye is a spheroidal organ located in the orbital cavity and protected by the eyelids and other ocular annexes [1]. Structurally, the eye consists of an internal compartment formed by the anterior and posterior chambers, iris, lens, vitreous cavity, retina, ciliary body, choroid, and intrinsic ocular muscles; and of an external compartment comprising the conjunctiva, the cornea, the sclera, and the tear film [2]. The internal compartment, physically separated from the immune system by the eye's blood–retinal barrier, maintains a sterile environment [3]. In contrast, the outer compartment of the eye is exposed to the external environment and, therefore, is susceptible to contamination with potentially pathogenic microorganisms [4][5][6]. Mechanical, anatomical, and immunological defense mechanisms have evolved to protect the ocular surface from many external agents [7]. The stability potential of the eye plays a central role in repelling aerosol particles near the surface of the eye [8]. In order to prevent attack by pathogenic microbial species, the eye possesses several defense mechanism, such as the production of a tear film containing several antimicrobial components—including lactoferrin, defensins, and lysozymes—that help to prevent colonization by pathogens, the presence of the conjunctiva as a physical and biological barrier to external environments, the existence of an innate immune response of the ocular surface epithelium that recognizes only potential pathogens' antigens and, finally, the presence of a commensal microbiota that constitutes the “barrier population” against pathogenic microbes [9][10][11]. The colonization of the ocular surface by commensal microorganisms has been confirmed by several studies [12][13]. The ocular surface of healthy individuals possesses a native microbiome that includes both viral and bacterial communities [14]. The ocular microbiota is widely known. Several studies have revealed a considerable complexity in the composition of the ocular microbiota, consisting of about 221 bacterial species. The most abundant phyla are represented by Proteobacteria, Actinobacteria, and Firmicutes [12][15]. Few studies have reported on the ocular virome. In the

vitreous fluids of healthy individuals, the major viral families found include Myoviridae, Siphoviridae, Phycodnaviridae, Herpesviridae, Poxviridae, Iridoviridae, Podoviridae, Retroviridae, Baculoviridae, and Flaviviridae [14]. Viral and bacterial agents coexist in equilibrium with the host in immunocompetent individuals and play a crucial role in maintaining the homeostasis of the eye's surface. The alteration of this ecosystem through various routes—such as poor hand hygiene, traumatic injuries, surgery, the transplacental route, the improper use of contact lenses, or the anatomical proximity and cellular receptor distribution between ocular and respiratory or nervous tissues—can promote the invasion of potentially pathogenic external microorganisms [16][17] and the alteration of the microbiota.

The majority of eye infections are attributed to bacteria, although viruses, fungi, and parasites can also contribute to ocular pathogenesis [18][19]. Among Gram-negative bacteria, the genus *Pseudomonas* is the most represented, while among the Gram-positive strains, Staphylococci are of considerable importance [20][21]. *Fusarium* spp. infections and *Candida albicans* and *Aspergillus* spp. endophthalmitis are also worth mentioning. With regard to viral infections, respiratory viruses such as human adenovirus (species D), avian influenza virus (H7), herpesviruses, coronaviruses, and arboviruses can cause conjunctivitis and/or keratoconjunctivitis [22][23]. The conjunctiva is therefore considered an optimal route of entry for respiratory viruses, and infected tears and conjunctival secretions can lead to the spread of infections [24].

2. Ocular Infection

Types of Ocular Infection

Blepharitis is an inflammation that affects the eyelid margin at the level of the eyelash implant; rather frequently, it tends to become chronic and relapse. Different forms have been distinguished, including hyperemic, seborrheic, scaly, and ulcerative blepharitis. The etiology is often bacterial. It is an infection of the ciliary follicle, often caused by *Staphylococcus aureus* or *S. epidermidis*, but sometimes it can be secondary to the presence of a mite (*Demodex folliculorum*), followed by an allergic reaction and secondary infection by bacteria that invade the hair follicle [25].

Dacryocystitis is an infection of the lacrimal sac, usually secondary to an inflammatory process of the nasal meatus or to a patency defect of the nasolacrimal duct that leads to stagnation of tear fluid. The onset of symptoms consists of copious tearing and conjunctival hyperemia, with discharge of purulent material from the lacrimal points; there may also be swelling of the lacrimal sac area [26].

Conjunctivitis is an inflammatory process of the mucous membrane that covers a large part of the anterior aspect of the eyeball and the posterior surface of the eyelids. The conjunctival sac, directly exposed to the external environment, is easily attacked by irritating factors (e.g., chemical, physical, allergens), but above all by infectious agents. Infectious conjunctivitis is very common and represents one of the most important eye diseases. The occurrence of this infectious state can be a consequence of certain erroneous behaviors (e.g., close contact with infected individuals, the possibility of touching contaminated hands, etc.) that expose the ocular conjunctiva to

pathogens. A variety of evidence indicates that the rate of bacterial conjunctivitis is about 50%. Another study reported that bacteria are responsible for only 50% of cases of suspected bacterial conjunctivitis. Conversely, a study reported that up to 52% of cases treated as viral conjunctivitis turned out to be bacterial conjunctivitis following the culture examination [27].

Keratitis is an inflammatory process of the corneal tissue. Excluding forms caused by physical (e.g., UV rays) and chemical agents (e.g., acids and alkalis), most cases of keratitis (about 80%) have an infectious etiology. The causative agents of infection can be bacteria, viruses, fungi, and/or protozoa. Currently, in countries where water purified of biological pollutants is available, infections with pyogenic bacteria are rare. However, because of the spread of soft contact lenses, the frequency of infectious keratitis caused by bacteria and fungi that contaminate the containers and liquids used for storage has increased [28].

Trachoma is a severe form of chronic keratoconjunctivitis and is the leading cause of blindness in some developing countries. It is caused by *Chlamydia trachomatis*, and its defining pathological characteristic is the formation of inclusion bodies called Halberstaedter–Prowazek bodies [29].

Infectious scleritis is an isolated acute inflammation of the sclera—the opaque fibrous membrane that makes up five-sixths of the outer tunic of the eyeball. Clinically, it manifests with severe pain and red eye. Scleritis and episcleritis are generally rarely caused by infectious agents. Despite this, diffuse scleritis is reported in some cases of tuberculosis and herpes zoster. Episcleritis generally has a benign, self-limited course, while scleritis can result in a thinning of the sclera and, sometimes, in staphyloma [30].

Infectious endophthalmitis is a suppurative process of the vitreous body, with a tendency to abscess and spread to other eye districts. The responsible microorganisms are mainly bacteria, but also fungi [31]. Among the Gram-positive bacteria, coagulase-negative Staphylococci, *S. aureus*, *Streptococcus* spp., and *Enterococcus* spp. are the leading causes of endophthalmitis. Of the Gram-negative bacteria, *Pseudomonas* spp., *K. pneumoniae*, and *E. coli* are the most representative. Of the fungi involved in these pathologies, the genera *Candida*, *Fusarium*, and *Aspergillus* are involved in endophthalmitis cases.

Uveitis is an inflammation state of part or all of the middle (vascular) layer of the ocular wall. The inflammatory phenomena can be of an autoimmune or infectious nature, with simultaneous involvement of the adjacent ocular portions (i.e., the sclera, cornea, and retina). In particular, it is possible to distinguish (i) anterior uveitis, which can affect the iris (iritis), the ciliary body (cyclitis), or both (iridocyclitis); and (ii) posterior uveitis, which can involve the choroid (choroiditis), the retina (retinitis), or both (chorioretinitis). Sometimes, retinal vasculitis with possible involvement is also observed in the posterior vitreous body [32]. The sites of ocular infections and associated etiological agents were shown in **Table 1**.

Table 1. Sites of ocular infections and associated etiological agents.

Site	Infection	Etiological Agents
Ocular surface	Conjunctivitis	Adenovirus, HSV, <i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., <i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i>
	Keratitis	HSV, VZV, <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus</i> spp., <i>Acanthamoeba</i> spp., <i>Candida</i> spp., <i>Aspergillus</i> spp.
	Episcleritis/scleritis	VZV, <i>Mycobacterium tuberculosis</i>
Internal eye	Anterior uveitis	HSV, VZV, CMV
	Intermediate and posterior uveitis	HSV, VZV, CMV, <i>Mycobacterium tuberculosis</i> , <i>Toxoplasma gondii</i> , <i>Treponema pallidum</i>
	Endophthalmitis	<i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Candida</i> spp., <i>Aspergillus</i> sp., <i>Fusarium</i> spp.
Eye annexes	Blepharitis	<i>Staphylococcus</i> spp., <i>Demodex folliculorum</i>
	Dacryocystitis	<i>Staphylococcus</i> spp.

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