International Journal of Infection
ISSN 1972-6945 / 2025 vol. 9, ISSUE N. 1, January-April

Article

OCULAR INFECTIONS CAN BE CAUSED BY BACTERIA, VIRUSES, FUNGI, OR PARASITES, LEADING TO AN IMMUNE RESPONSE AND INFLAMMATION

C. E. Gallenga[1*], P. Fazii[2] and P. Conti[3]

[1] Section of Ophthalmology, Department of Biomedical Sciences and Specialist Surgery, University of Ferrara, Ferrara, Italy;
[2] Microbiology Department, Pescara Hospital "Santo Spirito", Pescara, Italy;
[3] Immunology Department, Tufts University, Boston, USA.

**Correspondence to*:
Carla Enrica Gallenga,
Section of Ophthalmology,
Department of Biomedical Sciences and Specialist Surgery,
University of Ferrara,
44121 Ferrara, Italy.
e-mail: gllcln@unife.it

ABSTRACT

Ocular infections can be caused by microorganisms that provoke an innate and adaptive immune response, inflammation, and tissue damage. Microorganisms recognize pathogen-associated molecular patterns (PAMPs) and activate nuclear factor kappa B (NF-κB) and type I interferon (IFN) signaling, with the production of cytokines. Microorganisms can activate the complement fractions C3 and C5a, which cause opsonization of the pathogen and cell lysis. In the adaptive immune response, CD4+ helper cells and CD8+ cytotoxic cells are activated, which help eliminate the infection caused by the pathogen. Microorganisms initiate inflammation in ocular infections that is mediated by the cytokines TNF, IL-6, and IL-1β, which cause severe tissue damage. In addition, they activate macrophages and neutrophils to produce reactive oxygen species (ROS) and nitrous oxide (NO) to kill the pathogens, which causes damage to tissues. Infection by pathogenic microorganisms is fought by immune cells, including mast cells (MCs). These are cells that normally mediate allergic reactions through FcεRI receptors, but in the conjunctiva, cornea, and other ocular tissues, they play an important role in the pathophysiology of infections. Activation of MCs leads to phosphorylation of Syk kinase, triggering MAPK, PI3K, and NF-κB, with production of inflammatory cytokines. Inflammatory mediators released by MCs cause vasodilation, increased vascular permeability, and immune cell recruitment. Vascular endothelial growth factor (VEGF) contributes to neovascularization and worsens keratitis, while TNF is a cytokine that takes part in the inflammatory network. In viral conjunctivitis, viruses use certain receptor proteins, such as integrins, to enter the cell and activate the immune system. Activation of receptors triggers the NF-κB, IRF3, and IRF7 pathways, with production of IFNa and g and inflammatory cytokines. Super-inflammation leads to epithelial damage and can cause conjunctivitis. Bacterial conjunctivitis is mediated by the activation of TLR2 and 4 and inflammatory cytokines. Infectious keratitis is mediated by HSV-1, which enters the cell via nectin-1 and activates TLR3 and RIG-I, causing a TH1 immune response. Therapy includes NF-κB inhibitors, MAPK inhibitors, and MC stabilizers. The use of anti-inflammatory cytokines can certainly be helpful for treatment, although they are still under investigation.

KEYWORDS: *Ocular infection, microorganism, inflammation, immunity, keratitis, conjunctivitis, allergy*

Received: 06 January, 2025
Accepted: 06 March, 2025

1972-6945 (2025)

INTRODUCTION

Ocular infections can be caused by bacteria, viruses, fungi or parasites, which provoke an immune and inflammatory response (1). These reactions cause damage to ocular tissues that can be more or less severe depending on both the virulence of the microorganism and the immune response of the host (2) (Table I). Microorganisms can activate the innate and adaptive immune response (3). In the innate immune response, microorganisms recognize pathogen-associated molecular patterns (PAMPs), activating nuclear factor kappa B (NF-κB) and type I interferon signaling, which leads to the production of cytokines such as IL-1β, IL-6, IL-8, TNF (4). In NOD-like receptor (NLR) activation, inflammasomes are activated, promoting the release of IL-1β and IL-18, two potent cytokines that induce inflammation (5).

Table I. *Some common infectious eye diseases.*

Viral Infections:	Viral Conjunctivitis (Pink Eye)	Often caused by *Adenovirus*.
	Herpes Simplex Keratitis	Caused by *Herpes Simplex Virus (HSV-1)*.
	Herpes Zoster Ophthalmicus	Caused by *Varicella-Zoster Virus* (shingles in the eye).
	Molluscum Contagiosum	Viral skin infection that can affect the eyelid.
	Cytomegalovirus (CMV) Retinitis	A severe infection in immunocompromised individuals, such as those with HIV/AIDS.
Bacterial Infections:	Bacterial Conjunctivitis	Caused by bacteria like *Staphylococcus aureus*, *Streptococcus pneumoniae*, or *Haemophilus influenzae*.
	Blepharitis	Inflammation of the eyelids, often due to *Staphylococcus* infection.
	Keratitis	Infection of the cornea, often caused by *Pseudomonas aeruginosa* or *Staphylococcus aureus*.
	Endophthalmitis	Severe bacterial infection inside the eye, often after surgery or trauma.
Fungal Infections:	Fungal Keratitis	Often caused by *Fusarium*, *Aspergillus*, or *Candida* species.
	Endophthalmitis (Fungal)	Can be caused by *Candida* or *Aspergillus*.
Parasitic & Protozoal Infections:	Acanthamoeba Keratitis	Caused by *Acanthamoeba*, often linked to contact lens use.
	Toxoplasmosis	Caused by *Toxoplasma gondii*, affecting the retina (ocular toxoplasmosis).
	Onchocerciasis (River Blindness)	Caused by *Onchocerca volvulus*, transmitted by blackflies.
Chlamydial & Other Infections:	Trachoma	Caused by *Chlamydia trachomatis*, a leading cause of preventable blindness.
	Ophthalmia Neonatorum	Severe neonatal conjunctivitis due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.
	Syphilitic Uveitis	Caused by *Treponema pallidum* (syphilis).
	Leprosy-related Eye Disease	Caused by Mycobacterium leprae, affecting the eyelids and cornea.

Microorganisms activate complement fractions C3 and C5a, which together with membrane attack complexes (MAC), contribute to pathogen opsonization and cell lysis (6). In the adaptive immune response, CD4+ helper T cells (Th1, Th2, Th17) and CD8+ cytotoxic cells are activated, which help eliminate the infection caused by the microorganism (7). The acquired response also involves B cells with the production of IgA, IgG and IgM antibodies that neutralize pathogens and prevent adhesion to ocular surfaces (8). Tear antibody load increases in vaccinated patients (9).

Some pathogens induce specific infectious mechanisms, such as bacterial infections by Pseudomonas aeruginosa, or Staphylococcus aureus, where α-haemolysis and exotoxins are used to destroy the corneal epithelium (10). Viral infections such as Herpes Simplex Virus and Adenovirus use the host DNA replication machinery and induce apoptosis via interferon-stimulated genes (ISG) (11). SARS-Cov-2 enters conjunctival macrophages via the ACE-2 receptor or P2X7R (12). and activates the intracellular caspases by cross-talk with the NPL3 inflammasome, inducing the cytokine storm in the lung alveoli (13).

DISCUSSION

Microorganisms activate biological mechanisms of inflammation in ocular infections, such as the cytokines TNF, IL-6, and IL-1β that can cause a cytokine storm, leading to inflammation with severe tissue damage (14) (Fig.1). In addition, the production of reactive oxygen species (ROS) and nitric oxide (NO) induced by macrophages and neutrophils to kill pathogens can damage host cells (15). Released matrix metalloproteinases (MMPs) also contribute by damaging the extracellular matrix, causing corneal ulcers, as evidenced in bacterial keratitis (16).

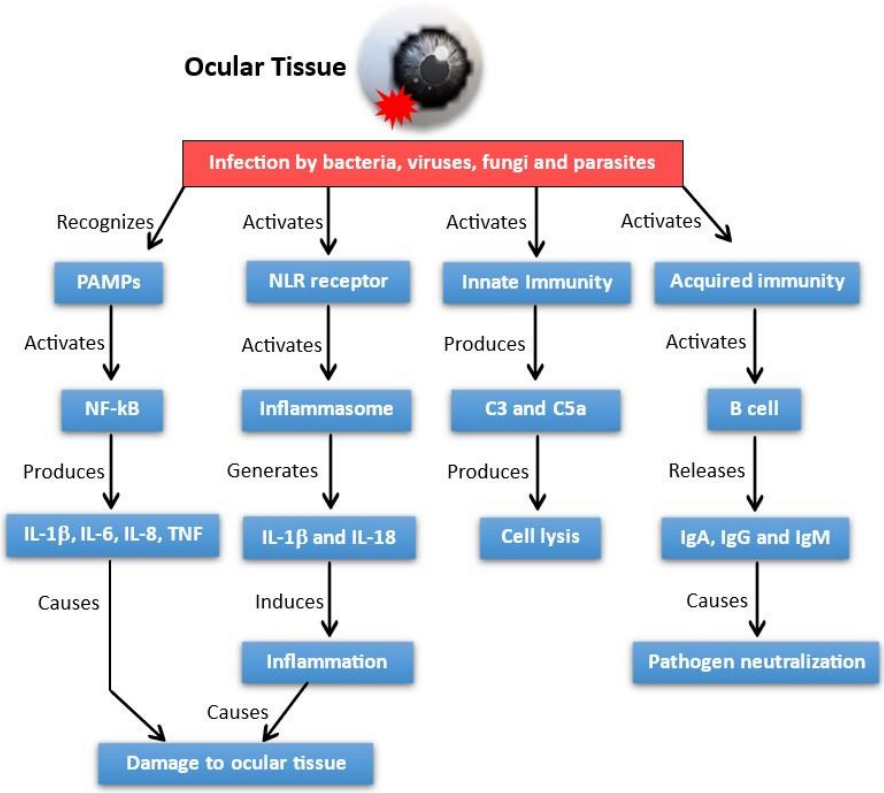

Fig. 1. *The biological mechanisms of inflammation in ocular infections induced by bacteria, viruses, fungi, and parasites.*

Fungal infections, such as *Candida*, activate the Dectin-1/Syk/CARD9 pathways, leading to chronic inflammation (17). In parasitic infections, particularly in Acanthamoeba, autophagy and excessive immune activation can be induced, which leads to serious keratitis (18). Microbial invasion triggers activation of immune cells, including mast cells (MCs) (19).

Role of mast cells (MCs) in eye infection

MCs are activated via FcεRI receptors when allergens cross-link IgE antibodies. MC activation leads to phosphorylation of Syk kinase, triggering downstream pathways such as MAPK, PI3K, and NF-κB, which mediate inflammatory responses (20). Preformed mediators such as histamine, tryptase, and and prostaglandins are released within seconds to minutes, while cytokines and chemokines such as IL-4, IL-5, IL-13, IL-1, IL-33, TNF, and CCL2 (MCP-1) promote the recruitment of eosinophils and Th2 cells (21).

MCs are tissue immune cells located in the conjunctiva, cornea, and other ocular tissues that play an important role in the pathophysiology of infections by mediating the inflammatory response (22). They are activated in response to pathogenic microorganisms such as bacteria, viruses, fungi, and parasites (23). MCs possess FceRI receptors that bind allergens and lead to degranulation with the release of inflammatory mediators. Pathogenic microorganisms bind to Toll-like receptors (TLRs) on MCs, generating and releasing pro-inflammatory cytokines (24). MCs contribute to the defense of the organism but can also cause damage to the body by releasing compounds that are harmful to tissues. Through TLRs, MCs recognize pathogens such as viruses and bacteria and become activated. Activation can lead to immediate degranulation with the release of inflammatory mediators such as histamine, and proteases, or to a delayed release with synthesis of pro-inflammatory cytokines and lipid mediators such as prostaglandins and leukotrienes (25). The

arachidonic acid cascade generates prostaglandins (including PGD_2, PGE_2) and leukotrienes (LTC_4, LTD_4, LTE_4), amplifying inflammation.

Inflammatory mediators released immediately after seconds cause vasodilation, increased vascular permeability and recruitment of immune cells (26). vascular endothelial growth factor (VEGF) contributes to neovascularization, worsening keratitis (27). TNF is a cytokine that can be stored in secretory granules and released immediately but can also be generated through protein synthesis and released later (28). All mediators released by MCs amplify the inflammatory response. The mitogen-activated protein kinase (MAPK) pathway is activated through TLR and cytokine receptors (29). These reactions lead to the production of pro-inflammatory cytokines (TNF, IL-6, IL-1β) and chemokines. The NF-κB pathway is activated by TLRs, with transcription of genes encoding inflammatory mediators.

PI3K-Akt regulates cell survival and inflammatory responses, and influences MC degranulation and cytokine release, while the JAK-STAT pathway activates cytokines IL-4 and IL-13 in allergic eye diseases (30). Other cytokine-producing cells, such as neutrophils, macrophages, and lymphocytes, are attracted to the site of infection, further amplifying the inflammatory state. Persistent inflammation can lead to systemic tissue damage and can also cause corneal damage and induce conjunctivitis or keratitis (31). Activated MCs not only mediate allergic conjunctivitis and keratitis, but are also involved in molecular and biological pathways, and can aggravate infections by viruses, bacteria and bacterial products, and fungi (32).

Conjunctivitis and keratitis are inflammatory eye diseases that affect the conjunctiva and cornea, respectively. They can be triggered by various infectious (bacterial, viral, fungal, parasitic) and non-infectious causes (allergic, autoimmune, chemical) (33). These diseases involve complex molecular and biological pathways that regulate inflammation, immune responses, and tissue damage. In infectious keratitis, MCs help recruit neutrophils and macrophages via TNF and IL-6, while in non-infectious keratitis (e.g., dry eye syndrome, autoimmune conditions), MCs contribute to chronic inflammation via the TGF-β and IL-17 pathways, leading to corneal damage (34). In allergic conjunctivitis, MC degranulation leads to vasodilation, vascular permeability, and itching, and activation of the histamine H1 receptor on the conjunctival epithelium and nerve endings, which also causes redness, swelling, and itching (35).

In viral conjunctivitis, viruses, including adenovirus, utilize CAR (Coxsackievirus and adenovirus receptor) and integrins for cell entry (36). Herpes simplex virus (HSV-1) binds to nectin-1 and heparan sulfate proteoglycans for entry, causing an immune and inflammatory response (37). Activation of pattern recognition receptors (PRRs) such as TLR3 for dsRNA, triggers the NF-κB, IRF3, and IRF7 pathways (11). These reactions induce type I interferons (IFN-α, IFN-β) and pro-inflammatory cytokines such as IL-6, IL-8, TNF, IFN-γ, while activation of dendritic cells enhances T cell responses (Th1, Th17) (38) (Fig.2).

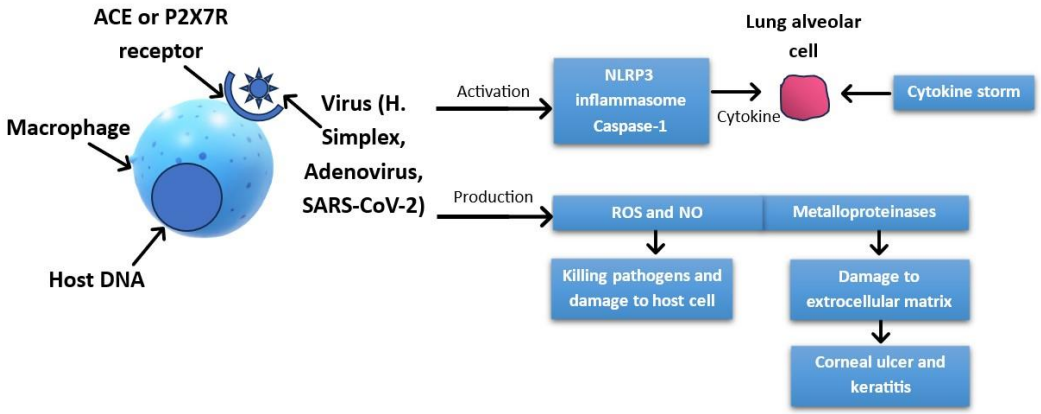

Fig. 2. *In viral conjunctivitis, macrophages can be activated through ACE or P2X7R receptors. This activates the NLRP3 inflammasome and caspase-1, which are precursors for the production of cytokines which cause a cytokine storm in the lungs. In addition, macrophage activation produces reactive oxygen species (ROS) and nitric oxide (NO) that kill pathogens but also damage the host cell. Metalloproteinases are generated by macrophages and damage the extracellular matrix and can cause corneal ulcers and keratitis.*

Overactive inflammation leads to epithelial damage and can cause pseudomembranous conjunctivitis (39). Bacterial conjunctivitis can be caused by several pathogens, including *S. aureus*, *S. pneumoniae*, *H. influenzae*, and *C. trachomatis* (39). These pathogens bind to their receptors via TLR2 and 4 and adhere to and invade tissues. Fimbriae, pili, and adhesins mediate bacterial attachment to the conjunctival epithelium, while *Chlamydia trachomatis* invades epithelial cells and forms intracellular inclusions (40).

In infectious keratitis due, for example, to HSV-1 or VZV enters via nectin-1, which establishes latency in the trigeminal ganglion (41). This leads to the activation of TLR3 and RIG-I which detect viral dsRNA (42). The hyperactive immune response via Th1 (IFN-γ, TNF) leads to corneal scarring, while type I IFNs (IFN-α, IFN-β) attempt to suppress viral replication. In bacterial keratitis due, for example, to *Pseudomonas aeruginosa* or *Staphylococcus aureus*, there is cell adhesion and biofilm formation (43). The bacteria use fimbriae and adhesins (e.g. type IV pili in Pseudomonas) for corneal adhesion. Biofilm formation via quorum sensing (LasR, RhlR) protects the bacteria (44). Bacteria can bind to TLR2 (Gram+) and TLR4 (Gram−), resulting in activation of the NLRP3 inflammasome (45).

The immune response is also mediated by Th17 cells that generate IL-17 and IL-22, cytokines that recruit neutrophils that fuel inflammation and lead to corneal damage (46). In neurotrophic keratitis, there is loss of corneal nerves, reduction of nerve growth factor (NGF), and delayed or failed healing.

Therapeutic targets may be inhibitors of NF-κB, MAPK, and MC stabilizers such as sodium cromoglicate, which may help modulate inflammation (47). Furthermore, anti-inflammatory cytokines including IL-10, TGF-β, IL-37 and IL-38, and regulatory pathways and lipid mediators such as lipoxins (products of the arachidonic acid cascade) may help improve the inflammatory state (48). Again, targeting MCs by blocking the H1 receptor or inhibiting them with sodium cromoglicate, results in a reduction of degranulation and, therefore, inflammation (35). VEGF inhibitors may help prevent corneal neovascularization in severe keratitis (49) (Fig.3). Inhibitors of inflammatory cytokines such as IL-37 and IL-38 are still the subject of clinical trials that need to be confirmed (50).

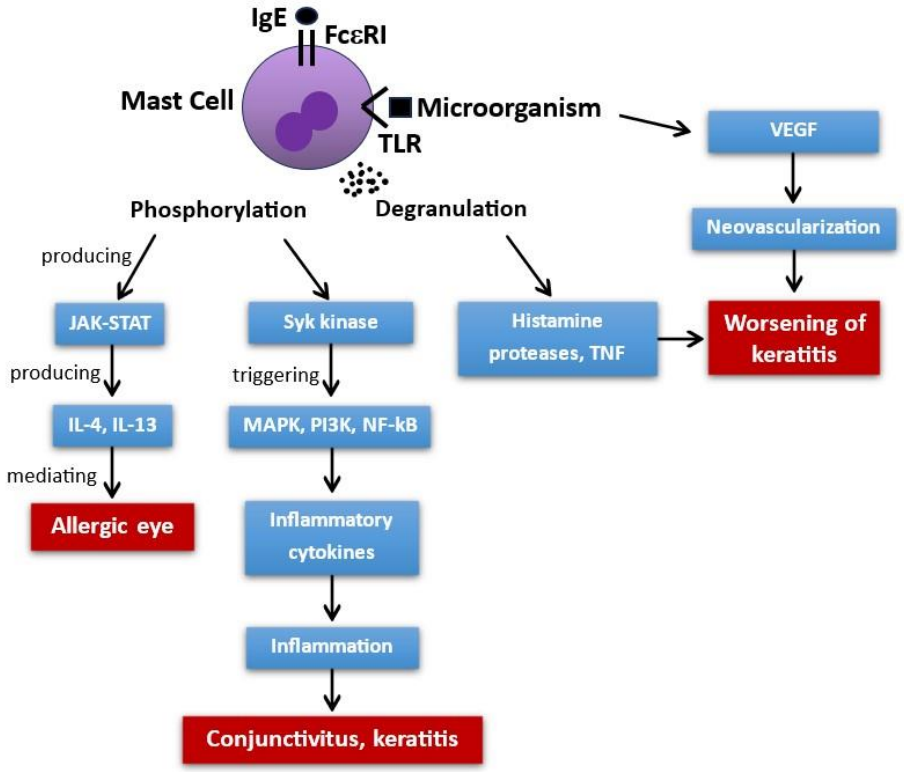

Fig. 3. *Mast cells (MCs) can be activated through several receptors including FcεRI and Toll-like receptors (TLRs). IgE binds FcεRI and induces MC degranulation within seconds, while the binding of microorganisms to the TLR causes the production of VEGF, which mediates neovascularization and leads to the worsening of keratitis. Following phosphorylation, MCs produce inflammatory cytokines that mediate allergic eye, conjunctivitis, and keratitis.*

CONCLUSIONS

Infectious ocular diseases involve complex interactions between pathogens, host immune responses, and tissue damage pathways. While viral infections are largely driven by IFN, bacterial infections rely on TLR-NF-κB signaling and immune cell recruitment. Fungal infections trigger Dectin-1/Th17 pathways, and allergic conjunctivitis follows a Th2-IgE-MC axis. These immune and inflammatory reactions can be regulated by cytokine inhibitors and immune modulators that can help target novel therapeutics and design new treatments.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Ting DSJ, Ho CS, Deshmukh R, Said DG, Dua HS. Infectious keratitis: an update on epidemiology, causative microorganisms, risk factors, and antimicrobial resistance. *Eye*. 2021;35(4):1084-1101. doi:https://doi.org/10.1038/s41433-020-01339-3
2. Kumar K, Askari F, Sahu M, Kaur R. Candida glabrata: A Lot More Than Meets the Eye. *Microorganisms*. 2019;7(2):39. doi:https://doi.org/10.3390/microorganisms7020039
3. Gilger BC. Immunology of the Ocular Surface. ˜ *The œVeterinary clinics of North America Small animal practice/Veterinary clinics of North America Small animal practice*. 2008;38(2):223-231. doi:https://doi.org/10.1016/j.cvsm.2007.11.004
4. Bryant-Hudson K, Conrady CD, Daniel J.J. Carr. Type I interferon and lymphangiogenesis in the HSV-1 infected cornea – Are they beneficial to the host? *Progress in Retinal and Eye Research*. 2013;36:281-291. doi:https://doi.org/10.1016/j.preteyeres.2013.06.003
5. Chen Y, Lai L, Mo Z, et al. Mulberry Leaf Extract Alleviates ***Staphylococcus aureus***-Induced Conjunctivitis in Rabbits via Downregulation of NLRP3 Inflammasome and Upregulation of the Nrf2 System and Suppression of Pro-Inflammatory Cytokines. *Pharmacology*. 2022;107(5-6):250-262. doi:https://doi.org/10.1159/000523786
6. Kotrajaras R, Tagami H. Corynebacterium pyogenes. *International Journal of Dermatology*. 1987;26(1):45-50. doi:https://doi.org/10.1111/j.1365-4362.1987.tb04575.x
7. Osorio Y, Homayon Ghiasi. Comparison of Adjuvant Efficacy of Herpes Simplex Virus Type 1 Recombinant Viruses Expressing T_H1 and T_H2 Cytokine Genes. *Journal of Virology*. 2003;77(10):5774-5783. doi:https://doi.org/10.1128/jvi.77.10.5774-5783.2003
8. Norcross EW, Sanders ME, Moore QC, et al. Active Immunization with Pneumolysin versus 23-Valent Polysaccharide Vaccine for *Streptococcus pneumoniae* Keratitis. *Investigative Ophthalmology & Visual Science*. 2011;52(12):9232-9232. doi:https://doi.org/10.1167/iovs.10-6968
9. Conti P, Stellin L, Caraffa A, et al. Advances in Mast Cell Activation by IL-1 and IL-33 in Sjögren's Syndrome: Promising Inhibitory Effect of IL-37. *International Journal of Molecular Sciences*. 2020;21(12):4297. doi:https://doi.org/10.3390/ijms21124297
10. Kreger AS. Pathogenesis of Pseudomonas aeruginosa Ocular Diseases. *Clinical Infectious Diseases*. 1983;5(Supplement_5):S931-S935. doi:https://doi.org/10.1093/clinids/5.supplement_5.s931
11. Lan W, Petznick A, Heryati S, Rifada M, Tong L. Nuclear Factor-κB: Central Regulator in Ocular Surface Inflammation and Diseases. *The Ocular Surface*. 2012;10(3):137-148. doi:https://doi.org/10.1016/j.jtos.2012.04.001
12. Ronconi G, Teté G, Kritas SK, et al. SARS-CoV-2, which induces COVID-19, causes kawasaki-like disease in children: role of pro-inflammatory and anti-inflammatory cytokines. *Journal of Biological Regulators and Homeostatic Agents*. 2020;34(3):767-773. doi:https://doi.org/10.23812/EDITORIAL-RONCONI-E-59
13. Rotondo JC, Martini F, Maritati M, et al. Advanced Molecular and Immunological Diagnostic Methods to Detect SARS-CoV-2 Infection. *Microorganisms*. 2022;10(6):1193. doi:https://doi.org/10.3390/microorganisms10061193

14. Cui B, Liu Y, Chen J, Chen H, Feng Y, Zhang P. Small molecule inhibitor CRT0066101 inhibits cytokine storm syndrome in a mouse model of lung injury. *International Immunopharmacology*. 2023;120:110240-110240. doi:https://doi.org/10.1016/j.intimp.2023.110240
15. Cerny O, Kamanova J, Masin J, Bibova I, Skopova K, Sebo P. Bordetella pertussis Adenylate Cyclase Toxin Blocks Induction of Bactericidal Nitric Oxide in Macrophages through cAMP-Dependent Activation of the SHP-1 Phosphatase. *The Journal of Immunology*. 2015;194(10):4901-4913. doi:https://doi.org/10.4049/jimmunol.1402941
16. García-López C, Rodríguez-Calvo-de-Mora M, Borroni D, Sánchez-González JM, Romano V, Rocha-de-Lossada C. The role of matrix metalloproteinases in infectious corneal ulcers. *Survey of Ophthalmology*. 2023;68(5):929-939. doi:https://doi.org/10.1016/j.survophthal.2023.06.007
17. Bihaniya H, Rudraprasad D, Joseph J. Pathobiology of Fungal Endophthalmitis: A Major Review. *ACS Infectious Diseases*. 2024;10(9):3126-3137. doi:https://doi.org/10.1021/acsinfecdis.4c00442
18. Moon EK, Kim SH, Hong Y, Chung DI, Goo YK, Kong HH. Autophagy Inhibitors as a Potential Antiamoebic Treatment for Acanthamoeba Keratitis. *Antimicrobial Agents and Chemotherapy*. 2015;59(7):4020-4025. doi:https://doi.org/10.1128/aac.05165-14
19. Royer DJ, Zheng M, Conrady CD, Carr DJJ. Granulocytes in Ocular HSV-1 Infection: Opposing Roles of Mast Cells and Neutrophils. *Investigative Opthalmology & Visual Science*. 2015;56(6):3763. doi:https://doi.org/10.1167/iovs.15-16900
20. Theoharides TC, Donelan JM, Papadopoulou N, Cao J, Kempuraj D, Conti P. Mast cells as targets of corticotropin-releasing factor and related peptides. *Trends in Pharmacological Sciences*. 2004;25(11):563-568. doi:https://doi.org/10.1016/j.tips.2004.09.007
21. Galli SJ, Kalesnikoff J, Grimbaldeston MA, Piliponsky AM, Williams CMM, Tsai M. mast cells as "tunable" effector and immunoregulatory cells: Recent Advances. *Annual Review of Immunology*. 2005;23(1):749-786. doi:https://doi.org/10.1146/annurev.immunol.21.120601.141025
22. Barone V, Scirocco L, Surico PL, et al. Mast cells and ocular surface: An update review. *Experimental Eye Research*. 2024;245:109982-109982. doi:https://doi.org/10.1016/j.exer.2024.109982
23. Bischoff SC, Krämer S. Human mast cells, bacteria, and intestinal immunity. *Immunological Reviews*. 2007;217(1):329-337. doi:https://doi.org/10.1111/j.1600-065x.2007.00523.x
24. Iwamura C, Nakayama T. Toll-like receptors in the respiratory system: Their roles in inflammation. *Current Allergy and Asthma Reports*. 2008;8(1):7-13. doi:https://doi.org/10.1007/s11882-008-0003-0
25. Arun S, Storan A, Myers B. Mast cell activation syndrome and the link with long COVID. *British Journal of Hospital Medicine*. 2022;83(7):1-10. doi:https://doi.org/10.12968/hmed.2022.0123
26. Bellomo RG, Gallenga CE, Caraffa A, Tetè G, Ronconi G, Conti P. Anaphylaxis is a rare reaction in COVID-19 vaccination. *Journal of Biological Regulators and Homeostatic Agents*. 2021;35(3):839-842. doi:https://doi.org/10.23812/BELLOMO_EDIT_3_21
27. Yun H, Yee MB, Lathrop KL, Kinchington PR, Hendricks RC, St AJ. Production of the Cytokine VEGF-A by CD4+ T and Myeloid Cells Disrupts the Corneal Nerve Landscape and Promotes Herpes Stromal Keratitis. *Immunity*. 2020;53(5):1050-1062.e5. doi:https://doi.org/10.1016/j.immuni.2020.10.013
28. Olszewski Maciej B, Trzaska D, Knol Edward F, Adamczewska V, Dastych J. Efficient sorting of TNF-alpha to rodent mast cell granules is dependent on N-linked glycosylation. *European Journal of Immunology*. 2006;36(4):997-1008. doi:https://doi.org/10.1002/eji.200535323
29. Yang H, Wei J, Zhang H, Lin L, Zhang W, He S. Upregulation of Toll-like receptor (TLR) expression and release of cytokines from P815 mast cells by GM-CSF. *BMC Cell Biology*. 2009;10(1). doi:https://doi.org/10.1186/1471-2121-10-37
30. Tang Y, Su R, Gu Q, Hu Y, Yang H. PI3K/AKT-mediated autophagy inhibition facilitates mast cell activation to enhance severe inflammatory lung injury in influenza A virus- and secondary Staphylococcus aureus-infected mice. *Antiviral Research*. 2022;209:105502-105502. doi:https://doi.org/10.1016/j.antiviral.2022.105502
31. Bernauer W, U Langenauer. Therapierefraktäre chronische (Kerato-)Conjunctivitis bei Kindern. *Klinische Monatsblätter für Augenheilkunde*. 2006;223(5):353-356. doi:https://doi.org/10.1055/s-2006-926557

32. Yutaka Omatsu, Shimizu Y, Haruki T, Inoue Y, Miyazaki D. Effect of atopic conditions on development and recurrences of infectious keratitis. *Allergology International*. 2024;73(3):445-452. doi:https://doi.org/10.1016/j.alit.2024.01.008
33. Origlieri C, Bielory L. Emerging drugs for conjunctivitis. *Expert Opinion on Emerging Drugs*. 2009;14(3):523-536. doi:https://doi.org/10.1517/14728210903103818
34. Ganeshan K, Bryce PJ. Regulatory T Cells Enhance Mast Cell Production of IL-6 via Surface-Bound TGF-β. *Journal of Immunology*. 2012;188(2):594-603. doi:https://doi.org/10.4049/jimmunol.1102389
35. Castillo M, Scott NW, Mustafa MZ, Mustafa MS, Azuara-Blanco A. Topical antihistamines and mast cell stabilisers for treating seasonal and perennial allergic conjunctivitis. *Cochrane Database of Systematic Reviews*. 2015;2015(6):CD009566. doi:https://doi.org/10.1002/14651858.cd009566.pub2
36. Amstutz B, Gastaldelli M, Kälin S, et al. Subversion of CtBP1-controlled macropinocytosis by human adenovirus serotype 3. *The EMBO Journal*. 2008;27(7):956-969. doi:https://doi.org/10.1038/emboj.2008.38
37. Holland EJ, Fingeret M, Mah FS. Use of Topical Steroids in Conjunctivitis. *Cornea*. 2019;38(8):1062-1067. doi:https://doi.org/10.1097/ico.0000000000001982
38. Manzouri B, Flynn T, Ohbayashi M, Ono SJ. The Dendritic Cell in Allergic Conjunctivitis. *The Ocular Surface*. 2008;6(2):70-78. doi:https://doi.org/10.1016/s1542-0124(12)70270-7
39. Thadasina M, Lim PP, Takhar J, Kuper-Sasse M, Zhang D. Pseudomembranous conjunctivitis caused by *Escherichia coli* in a newborn. *SAGE open medical case reports*. 2023;11:2050313X2311599-2050313X2311599. doi:https://doi.org/10.1177/2050313x231159964
40. Senn L, Hammerschlag MR, Greub G. Therapeutic approaches toChlamydiainfections. *Expert Opinion on Pharmacotherapy*. 2005;6(13):2281-2290. doi:https://doi.org/10.1517/14656566.6.13.2281
41. Ahmad I, Wilson DW. HSV-1 Cytoplasmic Envelopment and Egress. *International Journal of Molecular Sciences*. 2020;21(17):5969. doi:https://doi.org/10.3390/ijms21175969
42. Litt J, Cunningham AL, Arnalich-Montiel F, Parikh R. Herpes Zoster Ophthalmicus: Presentation, Complications, Treatment, and Prevention. *Infectious Diseases and Therapy*. 2024;13(7). doi:https://doi.org/10.1007/s40121-024-00990-7
43. Meager A, Visvalingam K, Peterson P, et al. Anti-Interferon Autoantibodies in Autoimmune Polyendocrinopathy Syndrome Type 1. *PLOS Medicine*. 2006;3(7):e289-e289. doi:https://doi.org/10.1371/journal.pmed.0030289
44. Worthington RJ, Richards JJ, Melander C. Small molecule control of bacterial biofilms. *Organic & Biomolecular Chemistry*. 2012;10(37):7457. doi:https://doi.org/10.1039/c2ob25835h
45. Leonardi A, Daull P, Garrigue JS, et al. Conjunctival transcriptome analysis reveals the overexpression of multiple pattern recognition receptors in vernal keratoconjunctivitis. *The Ocular Surface*. 2020;19:241-248. doi:https://doi.org/10.1016/j.jtos.2020.09.009
46. Oboki K, Ohno T, Saito H, Nakae S. Th17 and Allergy. *Allergology International*. 2008;57(2):121-134. doi:https://doi.org/10.2332/allergolint.r-07-160
47. Chen JJ, Zhang LN, Wang HN, et al. FAK inhibitor PF-431396 suppresses IgE-mediated mast cell activation and allergic inflammation in mice. *Biochemical Pharmacology*. 2021;192:114722-114722. doi:https://doi.org/10.1016/j.bcp.2021.114722
48. Pacharn P, Vichyanond P. Immunomodulators for conjunctivitis. *Current Opinion in Allergy and Clinical Immunology*. 2013;13(5):550-557. doi:https://doi.org/10.1097/aci.0b013e328364d86a
49. Ben Ghezala I, Gabrielle PH, Sibert M, et al. Severe intraocular inflammation after intravitreal injection of faricimab: a single-site case series of six patients. *American Journal of Ophthalmology*. 2024;269:11-19. doi:https://doi.org/10.1016/j.ajo.2024.08.008
50. Garlanda C, Dinarello CA, Mantovani A. The Interleukin-1 Family: Back to the Future. *Immunity*. 2013;39(6):1003-1018. doi:https://doi.org/10.1016/j.immuni.2013.11.010