# CHAPTER 16

# COMPLICATIONS OF CONTACT LENS WEAR

Contact lenses are foreign bodies placed on the eye. They can therefore initiate a classical immune response with all its sequelae [341]. It is important to have a basic understanding of the human bodies' inflammatory response as well as ocular immunology. This chapter will cover the basics of immunology before discussing common complications of contact lens wear. The reader is encouraged to review immunology in more detail using appropriate text books.

The immune system originated as a means of protecting the body from pathogenic organisms including viruses, bacteria, fungi, protozoans and multicellular parasites, as well as from cancerous cell growth. It consists of two functional divisions that act together to prevent infection. These divisions are the innate, natural or non-adaptive immune system, and the adaptive or specific immune system [342, 343].

## INNATE OR NATURAL, NON-ADAPTIVE IMMUNE SYSTEM [342, 343]

The innate system has a limited capacity to distinguish between pathogens; it has a stereotypical response to the pathogens; and an absence of memory meaning that the response is not enhanced by previous exposure to the pathogen. The innate system relies on physical and chemical barriers. The physical barriers include the skin, conjunctiva, and mucous membranes surrounding the respiratory, gastrointestinal, urinary and reproductive tracts. For an infectious agent to enter the body, an epithelial barrier must be breached. The biochemical barriers include; mucous and serous secretions containing antimicrobial compounds, such as lysozyme, lactoferrin, beta-lysin and various complement proteins, which cover the conjunctival and corneal epithelia. Similar constituents are found in the fluid overlying the respiratory and gastrointestinal mucosa. Lactic acid produced by bacteria in the female reproductive tract and acid produced in the stomach protect these regions from bacterial growth.

In addition to the factors mentioned above, a host of serum proteins, or acute phase proteins, are secreted by the liver and increase rapidly in concentration in response to infection. These proteins include; C-reactive protein; type 1 interferon and the complement proteins. C-reactive protein binds to bacteria and fungi facilitating their uptake by phagocytic cells. This process is known as opsonisation. Certain complement proteins can act as opsonins as well as antibodies, forming part of the adaptive immune response. Type 1 interferon can be divided into IFN-α and IFN-ß. IFN-α is secreted by mononuclear phagocytes and IFN-ß by fibroblasts. These factors play a role in limiting the spread of viral infections. Type 1 interferon also increase the activity of natural killer cells (NK), which play a surveillance role in innate immunity by seeking out virally infected cells and killing them in less time than it would take cytotoxic T cells to do the same.

The complement proteins circulate in the blood and are also present in the extracellular tissues. These proteins mediate five effector functions present in both the innate and adaptive immune response. These elements are:

- Osmotic lysis of bacteria on body cells by polymerisation into a pore structure – innate system
- Opsonisation of microorganisms facilitating their phagocytosis by macrophages and neutrophils – innate system
- Chemotactic attraction of leukocytes to a site of infection – innate system

- Solubilisation of immune complexes preventing hypersensitivity reaction – adaptive system
- Promoting the localisation of antigens to antibody-producing B lymphocytes and antigen-presenting cells – adaptive system

Inflammatory cells, such as macrophages and polymorphonuclear neutrophils, play an important role in innate immunity by phagocytosing a wide variety of foreign microorganisms and eliminating them. Both macrophages and neutrophils have antibodies and complement receptors. They therefore play a role in opsonisation. Both migrate to and accumulate at sites of complement activation in response to chemotactic agents. The specific process by which these circulating blood cells insinuate themselves between neighbouring endothelial cells to access the underlying tissues, is referred to as diapedesis.

Neutrophils belong to a group of blood cells called granulocytes. Granulocytes also include eosinophils and basophils. Neutrophils contain granules of lysozyme and lactoferrin. Eosinophils contain granules of major basic protein, eosinophil peroxidase, eosinophil cationic protein and eosinophil-derived neurotoxin. Eosinophils can be phagocytic, but their major role in the immune response is towards parasites and in certain types of allergic reactions. Basophils contain granules of heparin and leukotrienes, which when released, mediate systemic anaphylaxis.

Mast cells are found in mucus membranes and connective tissues and are important for wound healing and defence against pathogens via the inflammatory response. When mast cells are activated, they release cytokines, molecules that are used for cell signalling or cell-to-cell communication. Cytokines are similar to chemokines, meaning they can be used to communicate with neighbouring or distant cells about initiating an immune response. Cytokines are also used to trigger cell trafficking or movement to a specific area of the body. Chemokines are types of cytokines that are released by infected cells. Infected host cells release chemokines, to initiate an immune response and to warn neighbouring cells of the threat. Mediators such as histamine, cause blood vessels to dilate, increasing blood flow and cell trafficking to the area of infection. The cytokines released during this process act as a messenger service, alerting other immune cells, like neutrophils and macrophages to make their way to the area of infection, or to be on alert for circulating threats.

Dendritic cells are antigen-presenting cells located in the tissues, and can contact external environments through the skin, the inner mucosal lining of the nose, lungs, stomach and intestines. Since dendritic cells are located in the tissues that are common points for initial infection, they can identify threats and act as messengers for the rest of the immune system by antigen presentation. Dendritic cells also act as bridge between the innate immune system and the adaptive immune system.

## ADAPTIVE, ACQUIRED OR SPECIFIC IMMUNE SYSTEM [342, 343]

The adaptive immune system, also called acquired immunity, uses specific antigens to strategically mount an immune response. Unlike the innate immune system, which attacks only based on the identification of general threats, the adaptive immunity is activated by exposure to pathogens. It has the ability to distinguish between pathogenic organisms and uses an immunological memory to learn about the threat and enhance the immune response accordingly. The adaptive immune response is much slower to respond to threats and infections than the innate immune response, which is primed and ready to fight at all times. Constituents of the adaptive immune system include; T and B lymphocytes, antigen-presenting cells (APCs) and plasma cells.

Both T cells and B cells are lymphocytes that are derived from specific types of stem cells in the bone marrow. They are called multipotent hematopoietic stem cells. After they are made in the bone marrow, the cells need to mature and become activated. Each type of cell follows different paths to their final and mature forms.

### B Cells

After formation and maturation in the bone marrow, the naive B cells move into the lymphatic system to circulate throughout the body. In the lymphatic system, naive B cells encounter an antigen which starts the maturation process for the B cell. Antigens are anything that causes an immune response. Antigens can be entire pathogens, like bacteria, viruses, fungi and parasites, or smaller proteins that pathogens express. Antigens are like a name tag for each pathogen that announce the pathogens' presence to your immune system. Some pathogens are general, whereas others are very specific. A general antigen would announce "I'm dangerous", whereas a specific antigen would announce "I'm a bacteria, that will cause an infection in your gastrointestinal tract" or "I'm the influenza virus". B cells each have one of millions of distinctive surface antigen-specific receptors that are inherent to the organism's DNA. For example, naive B cells express antibodies on their cell surface, which can also be called membrane-bound antibodies. When a naive B cell encounters an antigen that fits or matches its membrane-bound antibody, it quickly divides to become either a memory B cell or an effector B cell, which is also called a plasma cell. Antibodies can bind to antigens directly. The antigen must effectively bind with a naive B cell's membrane-bound antibody, to differentiate or start the process of becoming one of the new forms of a B cell. Memory B cells express the same membrane-bound antibody as the original naive B cell or the "parent B cell". Plasma B cells produce the same antibody as the parent B cell, but they aren't membrane bound. Instead, plasma B cells can secrete antibodies. Secreted antibodies work to identify free pathogens that are circulating throughout the body. When the naive B cell divides and differentiates, both plasma B cells and memory B cells are made. B cells also express a specialised receptor, called the B cell receptor (BCR). B cell receptors assist with antigen binding, as well as internalisation and processing of the antigen. B cell receptors also play an important role in signalling pathways. After the antigen is internalised and processed, the B cell can initiate signalling pathways, such as cytokine release, to communicate with other cells of the immune system.

### T Cells

Once formed in the bone marrow, T progenitor cells migrate to the thymus to mature and become T cells. While in the thymus, the developing T cells start to express T cell receptors (TCRs) and other receptors called CD4 and CD8 receptors. All T cells express T cell receptors, either CD4 or CD8, but not both. Therefore, some T cells will express CD4 and others will express CD8. Unlike antibodies, which can bind to antigens directly, T cell receptors can only recognise antigens that are bound to certain receptor molecules, called major histocompatibility complex class 1 (MHCI) and class 2 (MHCII). These MHC molecules are membrane-bound surface receptors on antigen-presenting cells, like dendritic cells and macrophages. CD4 and CD8 play a role in T cell recognition and activation by binding to either MHCI or MHCII. T cell receptors have to undergo a process called rearrangement, causing the nearly limitless recombination of a gene that expresses antibodies. The process of rearrangement allows for a lot of binding diversity. This diversity could potentially lead to accidental attacks against self-cells and molecules because some rearrangement configurations can accidentally mimic a person's self-molecules and proteins. Mature T cells should recognise only foreign antigens combined with self-MHC molecules to mount an appropriate immune response. To make sure T cells will perform properly once they have matured and have been released from the thymus, they undergo two selection processes:

- Positive selection ensures MHC restriction by testing the ability of MHCI and MHCII to distinguish between self and non-self-proteins. To pass the positive selection process, cells must be capable of binding only self-MHC molecules. If these cells bind non-self-molecules instead of self-MHC molecules, they fail the positive selection process and are eliminated by apoptosis
- Negative selection tests for self-tolerance, tests the binding capabilities of CD4 and CD8 specifically. The ideal example of self-tolerance is when a T cell will only bind to self-MHC molecules presenting a

foreign antigen. If a T cell binds, via CD4 or CD8, a self-MHC molecule that isn't presenting an antigen or a self-MHC molecule that presenting a self-antigen, it will fail negative selection and be eliminated by apoptosis

These two selection processes are in place to protect our own cells and tissues against our own immune response. Without these selection processes, autoimmune diseases would be much more common.

After positive and negative selection, we are left with three types of mature T cells; Helper T cells ($T_H$), Cytotoxic T cells ($T_C$) and T regulatory cells ($T_{reg}$). $T_H$ cells express CD4 and help with the activation of $T_C$ cells, B cells and other immune cells. $T_C$ cells express CD8 and are responsible for removing pathogens and infected host cells. $T_{reg}$ cells express CD4 and another receptor, called CD25. $T_{reg}$ cells help distinguish between self and non-self-molecules and by doing so, reduce the risk of autoimmune diseases.

**HUMORAL VS. CELL MEDIATED IMMUNITY [342, 343]**

Immunity refers to the ability of your immune system to defend against infection and disease. There are two types of immunity that the adaptive immune system provides, and they are dependent on the functions of B and T cells described previously.

*Humoral immunity* is immunity from serum antibodies produced by plasma cells. More specifically, someone who has never been exposed to a specific disease can gain humoral immunity through administration of antibodies from someone who has been exposed and survived the same disease. "Humoral" refers to the bodily fluids, where these free-floating serum antibodies bind to antigens and assist with elimination.

*Cell-mediated immunity* can be acquired through T cells from someone who is immune to the target disease or infection. "Cell-mediated" refers to the fact that the response is carried out by cytotoxic cells. Much like humoral immunity, someone who has not been exposed to a specific disease can gain cell-mediated immunity through the administration of $T_H$ and $T_C$ cells from someone that has been exposed and survived the same disease. The $T_H$ cells act to activate other immune cells, while the $T_C$ cells assist with the elimination of pathogens and infected host cells.

**IMMUNOLOGICAL MEMORY [342, 343]**

Because the adaptive immune system can learn and remember specific pathogens, it can provide long-lasting defence and protection against recurrent infections. When the adaptive immune system is exposed to a new threat, the specifics of the antigen are memorised, and we are prevented from getting the disease again. The concept of immune memory is due to the body's ability to make antibodies against different pathogens.

A good example of immunological memory is shown in vaccinations. A vaccination against a virus can be made using either active, but weakened or attenuated virus, or using specific parts of the virus that are not active. Both attenuated whole virus and virus particles cannot actually cause an active infection. Instead, they mimic the presence of an active virus to cause an immune response, even though there are no real threats present. By getting a vaccination, you are exposing your body to the antigen required to produce antibodies specific to that virus and acquire a memory of the virus, without experiencing illness.

Some breakdowns in the immunological memory system can lead to autoimmune diseases. Molecular mimicry of a self-antigen by an infectious pathogen, such as bacteria and viruses, may trigger autoimmune disease, due to a cross-reactive immune response against the infection. One example of an organism that uses molecular mimicry to hide from immunological defences is *Streptococcus* infection.

## INNATE IMMUNITY VS. ADAPTIVE IMMUNITY: A SUMMARY [342, 343]

The following chart compares and summarises the important parts of the innate and adaptive immune system:

**Table 40:** Innate vs. Adaptive immunity

| Attribute | Innate Immunity | Adaptive Immunity |
|---|---|---|
| **Response Time** | Fast: minutes or hours | Slow: days |
| **Specificity** | Only specific for molecules and molecular patterns associated with general pathogens or foreign particles | Highly specific! Can discriminate between pathogen vs. non-pathogen structures, and miniscule differences in molecular structures |
| **Major Cell Types** | Macrophages, Neutrophils, Natural Killer Cells, Dendritic Cells, Basophils, Eosinophils | T cells, B cells, and other antigen presenting cells |
| **Key Components** | Antimicrobial peptides and proteins, such as toxic granules | Antibodies |
| **Self vs. Non-self-Discrimination** | Innate immunity is based on self vs. non-self-discrimination, so it has to be perfect | Not as good as the innate immune system, but still pretty good at determining which is which. Problems in self vs. non-self-discrimination result in autoimmune diseases |
| **Immunological Memory** | None | Memory used can lead to faster response to recurrent or subsequent infections |
| **Diversity and Customisation** | Limited: Receptors used are standard and only recognise antigen patterns. No new receptors are made to adapt the immune response | Highly diverse: can be customised by genetic recombination to recognise epitopes and antigenic determinants. |

## Cytokines and Their Role in Mediation and Regulation of the Innate and Adaptive Immune System [342, 343]

**Table 41:** Cytokines

| Cytokine | Innate immune system | Adaptive immune system | Function |
|---|---|---|---|
| **Type 1 interferon** | Yes | No | Inhibit viral replication and facilitates lysis of virally infected cells |
| **Tumour necrosis factor** | Yes | | Induces endothelial cells at the infection site to express adhesion molecules which bind ligands on lymphocytes, monocytes, and neutrophils. The cells are activated to eliminate the triggering pathogen |
| **Interlukin-1** | Yes | Yes | Similar to tumour necrosis factor in innate system but in adaptive system plays a role in promoting T cell activation and enhancing growth of B cells |
| **Interlukin-2** | No | Yes | Principal cytokine responsible for the propagation of the immune response, inducing T cells to proliferate and promotes the production of other cytokines. It also promotes the growth and release of antibody by B cells and enhances cytolytic potential of NK cells |
| **Interleukin-4** | No | Yes | Chief cytokine involved in the secretion of antibody by B cells in response to T-dependent antigens. Plays a role in the production of IgE by B cells. Mast cells use cell-bound IgE as a trigger for granule release in the allergic response |
| **Chemokines** | Yes | No | Family of chemotactic cytokines |

*Contd…*

| Cytokine | Innate immune system | Adaptive immune system | Function |
|---|---|---|---|
| **Defensins** | Yes | | Small cationic particles found in phagocytes and the mucosa, they have antimicrobial properties through membrane permeabilisation. Also have a role in tissue inflammation and endocrine regulation |
| **Interferon-gamma** | No | Yes | Potent activator of mononuclear phagocytes upregulates class 1 and 2 MHC antigens on the surface of cells |
| **Transforming growth factor-beta** | No | Yes | Inhibits proliferation of T and B cells but does not block the activity of cytotoxic T cells. It also inhibits the activity of NK cells and macrophages |

## HYPERSENSITIVITY REACTIONS [342, 343]

Hypersensitivity applies to adaptive or acquired immune reactions that are exaggerated or inappropriately active and therefore result in tissue damage. These reactions generally occur after secondary exposure to the antigen. Five types of hypersensitivity reactions exist and most of them have been observed in the eye. The following table summarises the five hypersensitivity reactions.

**Table 42:** Types of hypersensitivity reactions

| Type of hypersensitivity | Mediators | Effector mechanism |
|---|---|---|
| **Type 1 - Immediate** | IgE | Mast cell mediator release |
| **Type 2 – Antibody-mediated** | IgM and IgG | Complement proteins Inflammatory cell mediators<br>Opsonisation<br>Antibody-dependent cell mediated cytotoxicity |
| **Type 3 – Immune complex disease** | IgM and IgG immune complexes | Complement proteins<br>Inflammatory cell mediators |
| **Type 4 – Delayed type** | APCs, CD4+ and CD8+ T cells | Activated macrophages |
| **Type 5 – Activating antibodies** | Anti-hormone receptor antibody | Activation of target cell |

### Type 1: Hypersensitivity Reactions

Triggered within minutes in response to environmental antigens such as pollens, spores, faeces of dust mites and animal dander. The classical example in the eye is seasonal allergic conjunctivitis. After entering the body, the allergen binds to a B cell, which processes it and then presents it to $T_H$ cells. The stimulated $T_H$ cell then releases IL-4 and IL-3, which stimulates the B cell to release IgE. The IgE then binds to the mast cell region. On re-exposure the antigen can bind on IgE and crosslink adjacent molecules: leading to the influx of $Ca^{++}$: mast cell degranulation and the release of mast cell granules containing histamine, serotonin and heparin. Mast cell degranulation also results in the activation of phospholipase $A_2$. Membrane arachidonic acid is liberated and converted to leukotrienes, prostaglandins and a platelet activating factors. These newly formed mediators act chemotactically and cause vasodilation and increased vascular permeability. After several hours a late phase of this reaction can occur with the release of tumour necrosis factor (TNF) and IL-1 from the mast cells and IL-5 from the $T_H$ cells. Under the influence of these cytokines; T cells, eosinophils and basophils accumulate at the site of antigen exposure. An example of a late phase reaction is eczema or atopic dermatitis and asthma in the lungs.

Prostaglandins are a complex group of fatty acids, formed as a result of cell membrane disturbance, that releases arachidonic acid. Prostaglandins are primarily released as a response to mechanical inflammatory stimuli. Prostaglandin syntheses (cyclooxygenase) is present in all ocular tissues, but due to the large number of mast cells found in the conjunctiva, higher concentrations are found in the conjunctiva. Prostaglandins are released into the anterior chamber by:

- Mechanical trauma
- Chemical injury
- Trigeminal nerve stimulation

This results in pupillary miosis due to smooth muscle contraction; hyperaemia; cells and flare due to blood-aqueous barrier breakdown; protein leaking into aqueous and elevation of intraocular pressure. High levels of prostaglandins are found in acute uveitis, after ocular trauma, after cataract extraction and other anterior segment surgeries.

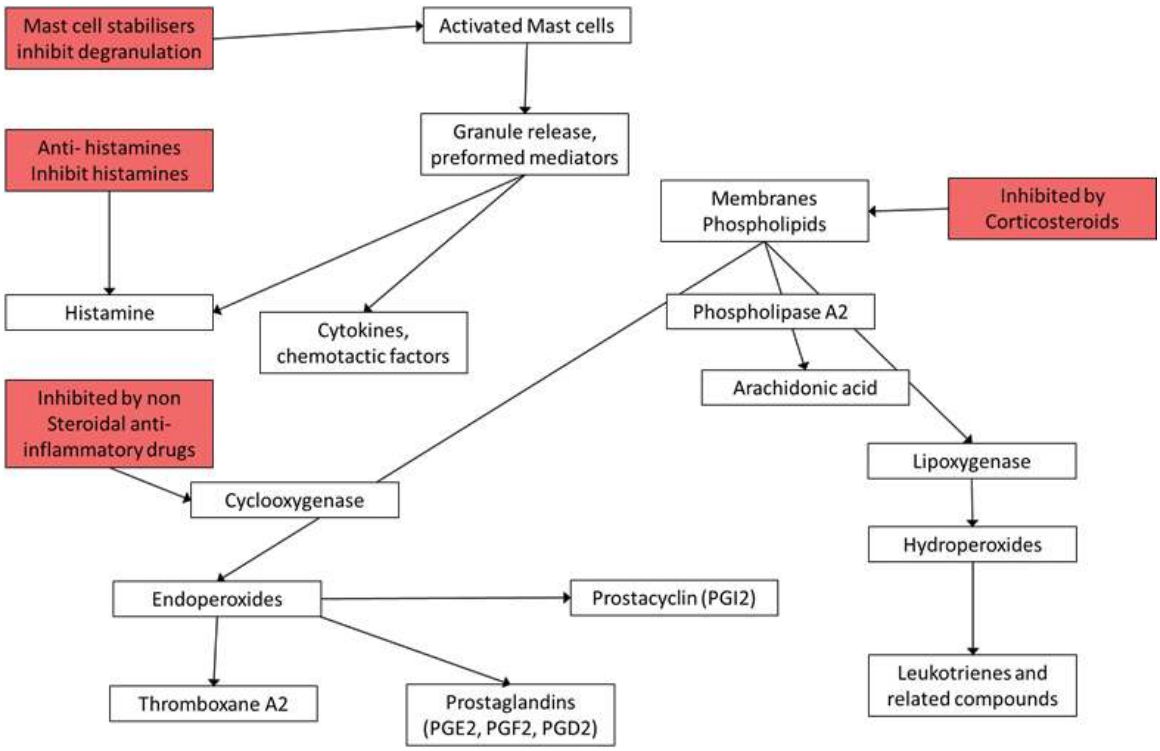


**Figure 73:** Aracidonic acid pathway and therapeutic intervention

### Type 2: Hypersensitivity Reactions

There are four basic effector mechanisms, in which antibodies are involved.

- Classical pathway complement activation resulting in the osmotic lysis of the target. Examples of hypersensitivity reactions that involve complement-mediated cell lysis, include the transfusion reaction, haemolytic disease of the new born and hyper acute graft rejection
- Recruitment and activation of inflammatory cells. An example of this type of reaction is Mooren's ulcer
- Phagocytosis of antibody-coated cells. An example of this type of reaction is autoimmune haemolytic anaemia
- Antibody-dependent cell-mediated cytotoxicity. An example of this type of reaction includes autoimmune thyroiditis

### Type 3: Hypersensitivity Reactions

Under the right conditions of stimulation, a multivalent antigen-antibody or immune complex forms. These immune complexes are generally removed effectively by mononuclear phagocytes, but if they persist their presence can trigger a hypersensitivity reaction. This can happen in persistent low-grade infection by microorganisms, such as streptococcal and staphylococcal bacteria, in autoimmunity, where continued production of autoantibodies leads to prolonged immune complex formation and deposition, and formation of immune complexes at body surfaces. For example, lung deposition following repeated inhalation of antigenic materials.

In high concentration, immune complexes deposit in the tissues, where they activate complement leading to the recruitment and activation of inflammatory cells, predominantly neutrophils. These cells then cause tissue injury. Examples of type 3 hypersensitivity reactions are vasculitis, nephritis and arthritis.

### Type 4: Hypersensitivity Reactions

Type 4 hypersensitivity reactions to protein antigens are delayed and take up to 12 hours to develop. Unlike other forms of hypersensitivity, type 4 cannot be transferred by serum, but can be transferred by T cells that have become sensitised to a specific antigen. These cells act in concert with other cell types that have been recruited to the site of the reaction.

Two types of type 4 hypersensitivity reactions occur. Contact hypersensitivity and the tuberculin reaction:

Contact hypersensitivity or contact dermatitis is restricted to the epidermal layer and is characterised by the development of eczema within 48 hours after exposure to the antigen. Allergens that induce this type of reaction include rubber, nickel, chromate and plant material. Initial immune cell infiltration occurs within 3 hours and consists of T cells and macrophages seen around the local vasculature in the dermis. This is followed by infiltration of the cells into the epidermis, where they act to eliminate the antigen within the next 2–3 days.

The tuberculin reaction is induced by soluble antigens from several organisms, including Mycobacterium and Listeria. The localised cutaneous reaction to these antigens is used as the basis for a test of exposure to these organisms, for example the TB test in the case of tuberculosis. T cells and macrophages play a role in antigen elimination, but in the tuberculin reaction the cells remain in the dermis. Induration or hardness is the hallmark of the tuberculin reaction, which is generally maximal at 48 hours after exposure.

Examples of type 4 delayed hypersensitivity reactions include; ocular allergy, corneal graft rejection, cosmetic-induced conjunctivitis, idiopathic uveitis and sympathetic ophthalmia. Systemic disease such as type 1 diabetes, encephalomyelitis and Chron's disease also have a delayed hypersensitivity component.

### Type 5: Hypersensitivity Reactions

This type of reaction is mediated by antibodies that bind to the surface hormone receptors and activate, rather than block intracellular signalling. An example includes the effect of thyroid stimulating autoantibody on the thyroid stimulating hormone receptor in Graves' disease.

## INFLAMMATION [344]

"Inflammation is the reaction of tissue to injury". Cornelius Celsus established the four principle signs of inflammation in the 1st century AD – "RUBOR et TUMOR cum CALORE et DOLORE" – Redness & swelling with heat & pain.

Redness & heat is caused by:

- Increased vascular dilation
- Internal immunological reactions

Swelling

- Results from increased capillary permeability

Pain results from

- Stretched nerve endings due to swelling
- Irritation to nerve endings by released inflammatory substances

Virchow added a 5th sign in 1882 - "FUNCTIO LAESA" – This refers to loss of function of inflamed tissue, mainly due to swelling & nerve fibre involvement. Inflammation can be caused by:

- Infectious microbes
- Mechanical trauma
- Chemical and thermal burns
- Toxic immune responses
- Innate and acquired immune responses

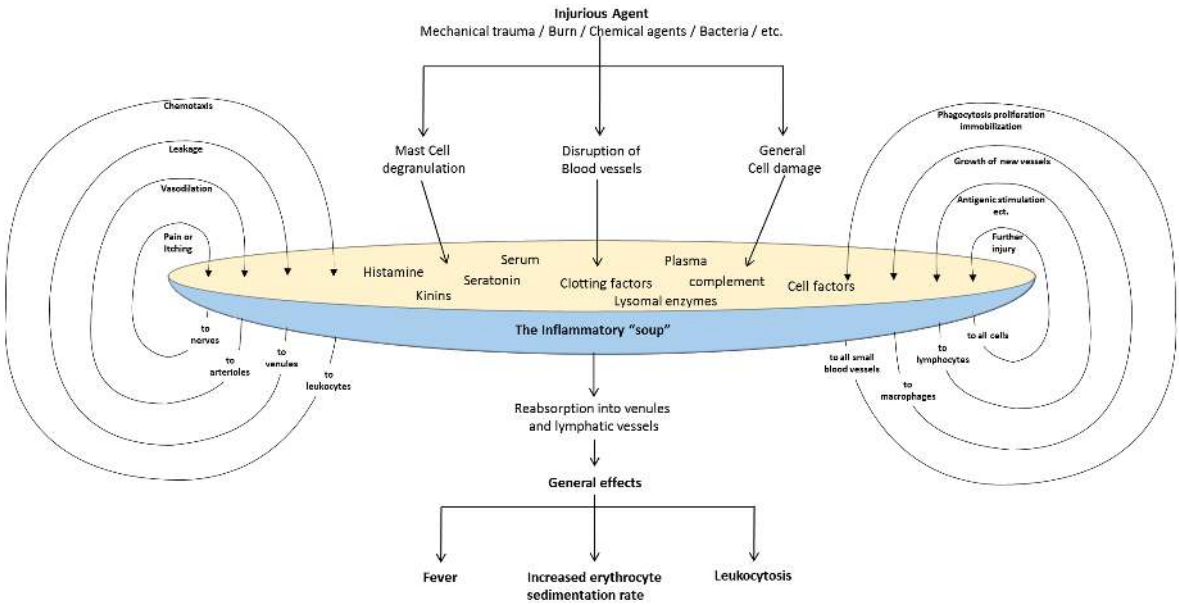


**Figure 74:** Inflammation [344]

## WHEN DEALING WITH C/L COMPLICATIONS THE FOLLOWING MNEMONIC IS HANDY TO REMEMBER

**"I'M A PSYCHO"**

I = Infectious / inflammatory reactions
M = Mechanical response
A = Allergic / hypersensitivity / immune reactions
P = Physiological response (tight lens syndrome)
S = Solution reactions
Y = Yearly replacement
C = Compliance with instructions
H = Hygiene - hands, lids, lenses and case
O = Other's - secondary systemic problems, sinusitis etc.

**When Dispensing Lenses Invite Your Patients To:**

**"RSVP"**

R = Return if Redness occur
S = Return if Sensitive to light (photophobia)
V = Return if Vision changes occur
P = Return if Pain occur

**Table 43:** Summary of the major contact lens complications and their aetiology

| **Contact lens complications by ocular structure and aetiology**<br>***Not all the listed complications are primarily caused by lens wear, but by definition, complicate lens wear and deserve attention*** |
|---|
| ***Lids***<br>**Mechanical:** Ptosis – associated with RGP application and removal or secondary to CLPC<br>**Toxic:** Solution reactions<br>**Immune mediated:** CLPC – Type 1 and type 4 hypersensitivity reactions and MGD<br>**Infectious:** Blepharitis |
| **Tear Layer**<br>**Mechanical:** Tear disruption due to contact lens and MGD<br>**Desiccation:** Contact lens mediated dry eye<br>**Immune mediated:** Sjörgens syndrome |
| **Bulbar conjunctiva**<br>**Mechanical:** Erosions leading to chemosis and vascular injection<br>**Toxic:** Solution-related chemosis and vascular injection, occasionally CL-SLK<br>**Desiccation:** Erosion and vascular injection<br>**Hypoxia:** Vascular injection<br>**Immune-mediated:** Vascular injection, CLARE<br>**Infectious:** Chemosis and vascular injection |
| **Corneal epithelium and anterior limiting lamina (Bowman's layer)**<br>**Mechanical:** 3 & 9 o'clock staining (can lead to either dellen or VLK), contact lens adhesion, binding rings and corneal distortion, SEALs, foreign body or damaged lens edge erosions and abrasions, soiled contact lens back surface, and dimple veil staining<br>**Desiccation:** 3 & 9 o'clock staining, inferior arcuate staining due to dehydration of soft lenses<br>**Toxic:** Pan-corneal staining, erosions due to medicamentosa<br>**Hypoxia:** Cluster staining, decreased mitosis leading to thinning, adhesion and sensitivity, microcysts and microcystic edema, oedematous corneal formations (ECF), and corneal distortion<br>**Immune-mediated:** Staining and erosion due to hypersensitivity reactions, as well as stem cell failure related pannus<br>**Infectious:** Primarily bacterial (most often ***Pseudomonas, Staphylococcal, Streptococcal***), also ***Acanthamoeba***; consider fungal and viral infections as well |
| **Corneal stroma**<br>**Toxic:** IK or AIK<br>**Hypoxia:** CCC, acute swelling (leading to stromal striae at 4 percent to 6 percent swelling and striate keratopathy at 10 percent swelling) and chronic thinning (through loss of glycosaminoglycans), warpage, sub-epithelial neovascularisation (pannus), deep stromal neovascularisation, and IK<br>**Immune-mediated:** IK, oedema<br>**Infectious:** Direct (MK) and indirect (CLPU) infiltrates, an oedema |
| **Corneal endothelium and posterior limiting lamina (Descemet's membrane)**<br>**Hypoxia:** Blebs (acute) and polymegathism (chronic) |

## HYPOXIA

Corneal hypoxia has probably been the most common complication of lens wear. Hypoxia causes corneal epithelial microcysts and microcystic oedema; corneal stromal oedema; decreased epithelial mitosis, sensitivity and adhesion; central corneal clouding (CCC); changes in stromal thickness; acidosis and striae as well as; endothelial blebs and polymegethism [22, 345–350]. Hypoxia can result in corneal distortion and warpage, which causes spectacle blur.

Corneal exhaustion syndrome causes previously successful long-term contact lens wearers to suddenly become intolerant [351]. Contact lens-driven hypoxia causes conjunctival vascular injection [36]. Superficial corneal pannus can be associated with hypoxia, as well as chronic mechanical 3 and 9 o'clock epithelial desiccation with RGPs [352, 353]. Deep stromal neovascularisation is another rare complication. Secondary intra-corneal haemorrhages can also occur with deep or superficial neovascularisation regardless of aetiology. Maintaining tear oxygen tension at about 100 mmHg will preclude clinically significant hypoxia. Modern lens materials with oxygen permeability of 50 to 100 Fatt units or greater should provide reasonable corneal oxygenation under daily wear conditions [32]. Lenses made from very high oxygen transmissible materials also appear to provide reasonable corneal oxygenation even when used for EW.

In summary, hypoxia directly impacts the corneal epithelium-, stroma- and endothelium physiology, causing corneal sensitivity and refraction changes, which are the most common contact lens complications. Indirectly, hypoxia can lead to epithelial keratitis, over wear abrasions, corneal infiltration, microbial keratitis and corneal neovascularisation.

**Table 44:** Acute and chronic effects of hypoxia

| | |
|---|---|
| **Acute complications of hypoxia** | ♦ Superficial punctate keratitis<br>♦ Epithelial oedema<br>♦ Epithelial healing<br>♦ Stromal swelling<br>♦ Endothelial blebs and Corneal pH<br>♦ Induced changes in corneal topography and refractive error |
| **Chronic effects of hypoxia** | ♦ Microcysts<br>♦ Epithelial thinning<br>♦ Corneal sensitivity<br>♦ Reduced stromal thickness<br>♦ Neovascularisation<br>♦ Endothelial polymegathism and reduced function<br>♦ Induced changes in corneal topography and refractive error |

## MECHANICAL/LID COMPLICATIONS

### Blinking

Blinking is a normal high speed, short duration closure of the eyelids (both superior and inferior) and could be spontaneous or reflex in nature. Reflex blinking can be elicited by a number of stimuli; such as strong lights; conjunctival and corneal touch; loud noise; approaching objects; as well as contact lens insertion and removal. Spontaneous blinking is accomplished mainly by the upper lid with the lower lid remaining nearly stationary. The orbicularis oculi muscle, innervated by the 7$^{th}$ cranial nerve, is mainly responsible for the blink [20]. Lid closure starts from the outer canthus and moves in a wave motion toward the inner canthus, forcing tears toward the puncta aiding in tear drainage [354]. This zipper like movement, typically affects the orientation of toric lenses. Hence, the common tendency of these lenses to rotate a few degrees nasally. The rate of spontaneous blinking is affected by the level of visual activity, emotional state as well as environmental factors such as the level of dryness and wind flow. The completeness of the blink is reduced with intense concentration, such as when doing computer work or reading. Ableson and Holly, 1977 classified blinking into four types [355].

- Complete blink – upper lid covers more than 67% of the cornea
- Incomplete blink – upper lid covers less than 67% of the cornea
- Twitch blink – small movement of the upper eyelid
- Forced blink – lower lid raises to complete eye closure

Complete blinks occur most frequently, followed by incomplete blinks with twitch and forced blinks making up the rest. The average compete blink rate was around 14.3 blinks per minute [20]. Spontaneous blinks serve the following functions [20].

- Maintenance of an intact tear film and spreading the tear film across the cornea
- Removal of debris from the tear film to the lacrimal system
- Facilitating of tear exchange by constantly swiping tears toward the puncta located at the inner canthus

## Effect of Contact Lenses on Blinking

### Blink Rate

Blink rate is increased (±21 blinks per minute) with RGP lenses due to the continual irritation caused by the edge of the lens on the lid margin. This alteration in blink rate is only evident while lenses are worn and returns to normal levels once the lenses are removed. With soft lenses the blink rate is closer to normal, but some authors did find an increase in blink rate [21].

### Blink Type

The inter-blink rate of long term RGP lens wearers was reduced, but the type of blink with RGP and soft lenses was not affected [21].

### Complications of Abnormal Blinking with Contact Lenses [21]

- Lens surface drying and deposits – As mentioned previously the tear film over the contact lens is different than that of the ocular tear film. The lipid layer is thinner or absent, the aqueous layer is of variable thickness, the tear film is less stable and the TBUT is reduced to between 3 and 10 seconds. This may lead to intermittent drying of the lens surface if the blink rate falls below the TBUT and depending on lens material subsequent deposits on the lens surface
- Visual degradation – Blink induced lens movement causes a reduction in visual performance that is potentially greater with toric rather than spherical contact lenses. The visual degradation is attributed to the prismatic shift of the retinal image induced by the movement of the lens due to the blink
- Prolonged lens settling – Lens settling, or degree of post-insertion movement is affected by blink rate. Slower blink rates (<10 blinks per minute) equals longer settling times
- Epithelial desiccation (SEALS) – This can occur with thin high-water contact lenses, but also with well-fitting high-water content hydrogel lenses. This is due to TBU at the inferior tear prism margin leading to drying of the lens and mechanical abrasion of the corneal epithelium
- Post-lens tear stagnation – Organic material, such as desquamated epithelial cells, microorganisms, mucus, proteins, lipids and inflammatory cells, as well as environmental material such as dust, pollen, atmospheric pollutants frequently occur in the tear film. This material is washed away constantly by the tear movement and blink to the lacrimal drainage system. With a contact lens in situ, the post lens tear film can stagnate leaving the pollutants in contact with the cornea. This leads to toxic, allergic, traumatic and infectious insult to the cornea and inflammation with all its sequelae. It is estimated that the tear exchange with well fitted RGP lenses is between 10 and 17% per blink, with soft lenses 1% per blink and with scleral lenses 0.2% per minute. Adequate lens movement is essential to avoid tear stagnation, adverse reactions and discomfort. Tear stagnation in daily wear lenses is of less concern than in extended wear lenses. However, if left uncorrected it can lead to the formation of a biofilm on the inside of the lens, which results in a host of toxic, infectious and inflammatory or immunological reactions

- Hypoxia and hypercapnia - Gaseous exchange is enhanced by blinking, lens movement and tear exchange. The distribution of oxygenated tears (tear mixing) is also affected by blinking and lens movement, which is especially important when fitting lenses of non-uniform thickness
- 3 and 9 o'clock staining – This is a common problem with RGP lenses and is due to lens-induced disturbance of the normal blink movement of the upper lid over the lens and the cornea. The RGP lens bridges the upper lid away from the cornea so that during the blink, the lid is unable to wet the bridged regions of the cornea, typically at the 3 and 9 o'clock positions. This leads to local drying, consequent staining and inflammation

**Management of Abnormal Blinking with Contact Lenses**

Clinicians have two options when dealing with abnormal spontaneous blinking caused by contact lens wear.

- Train patients to modify their blinking activity
- Modify the lens design and fit. For instance, changing from an RGP to a soft lens to alleviate 3 and 9 o'clock staining.

**Contact Lens Induced Lid Ptosis (CLIP)**

Ptosis is defined as "prolapse", abnormal depression or falling-down of an organ or part thereof. Ptosis is not only confined to the upper lid and therefore the correct terminology should be "blepharoptosis"[120]. Van der Bosch and Lemij, 1992 defines ptosis as a situation, where the distance between the centre of the pupil and the upper lid is <2.8 mm [356]. Ptosis can also be evaluated by measuring the gap between the skin fold of the upper lid and the lid margin, a larger gap indicating ptosis. In a normal patient, this gap is only slightly higher than the eyelid margin. CLIP can be bilateral or unilateral and associated with RGP wear. The aetiology of CLIP is associated with a number of mechanisms, which can be classified as either aponeurogenic, involving some form of dysfunction of the levator aponeurosis, or non-aponeurogenic [21].

**Figure 75:** Note the upper lid skin fold distance from the lid margin. This measured to evaluate lid ptosis

**Aponeurogenic [21]**

- Forced lid squeezing may cause increased traction of the levator aponeurosis leading to disinsertion or dehiscence
- Lateral eyelid stretching during lens removal and forced blinking can lead to stretching and thinning of the levator aponeurosis
- Rigid lens displacement of the tarsus, during removal of the lens, can exert pressure on the palpebral conjunctiva and the levator aponeurosis leading to stretching and thinning of the aponeurosis
- Blink induced rubbing can cause lens rubbing against lid structures, displacement of the lid away from the globe, as well as stretching and gradual thinning of the levator aponeurosis

**Non-Aponeurogenic [21]**

- Oedema – Constant irritation and trauma to the lid caused by an RGP lens can lead to a sub-clinical inflammation and subsequent oedema. The oedema leads to ptosis, due to physical enlargement of the lid in all dimensions and gravity lowers the lid
- Blepharospasm – RGP lenses are intrinsically uncomfortable, especially during adaptation, due to the constant bumping of the lens edge against the lid margins. Patients involuntary narrow their palpebral aperture to stabilise the lens and prevent bumping of the lens against the lid margin
- Papillary conjunctivitis – Severe papillary conjunctivitis is associated with inflammation, oedema and ptosis of the upper lids. This is more prevalent in soft lens wearers

**Management of CLIP [21]**

Management depends on the aetiology, aponeurogenic, non-aponeurogenic or papillary conjunctivitis. To differentiate between these causes may be difficult, but by ceasing lens wear for a period of at least 1–3 months, lid oedema and involuntary blepharospasm can be ruled out. Everting the lid will reveal the presence of papillary conjunctivitis. If ptosis persists after cessation of lens wear and the resolution of papillary conjunctivitis the cause is most likely aponeurogenic and surgical intervention may be needed.

**Mucin Balls**

Mucin balls, also referred to as pre-corneal deposits or "lipid plugs," appear in varying numbers in patients wearing both soft and rigid gas permeable lenses. They occur in higher numbers with certain lens materials, and certain patients. Increased frequency of mucin balls during high Dk silicone hydrogel lens wear has heightened interest in this phenomenon. Mucin balls form within minutes of lens insertion but appear to have no adverse effects on ocular health. They do not affect vision and comfort, and they are not associated with any adverse reactions. It is important to distinguish mucin balls from other ocular signs, which are similar in appearance, but indicate that a cornea is under hypoxic or other stress [357–359].

Measuring approximately 40 to 120 μm in diameter, mucin balls are relatively large, generally spherical bodies that we easily observe with the biomicroscope under direct white light illumination, as well as indirect and retro illumination. They differ from both vacuoles and microcysts, which are less visible, smaller in size, and require retro illumination to be viewed. Millar et al., 2003 analysed mucin balls and found that they are PAS positive, which indicates that they consist mainly of glycoproteins. Lipids and bacteria were absent and they concluded that mucin balls consisted exclusively of collapsed mucin [360]. Mucin balls remain motionless under the lens, even during blinking, and indent the corneal epithelial surface during contact lens wear [357–359]. Following lens removal, mucin balls tend to easily dislodge with blinking, leaving an imprint or depression in the cornea, which pools tear fluid and can therefore be seen upon instillation of NAFL. Fluorescein can also be used to distinguish between mucin balls and vacuoles, as the latter shows no response to fluorescein. Indentations resolve spontaneously between 30 minutes and several hours after lens removal [361, 362]. Occasionally mucin balls float briefly in the tear film, following lens removal. Mucin balls are found in significantly greater numbers in high Dk silicone hydrogel soft lens wearers. These results suggest that patient characteristics, as well as different lens types, predispose lens wearers to development of mucin balls [363].

**How do Mucin Balls Form?**

No definite aetiology has been established for the development of mucin balls. However, greater numbers of mucin balls are observed with lens materials of higher modulus. The relatively stiffer materials in high Dk silicone hydrogel lenses may exacerbate the mechanical interaction of the lens with the ocular surface.

One hypothesis is that lenses with specific surface characteristics can create shear and surface tension forces within the tear film. These forces cause the tear film (mucin) to roll into beads as the lens moves over the ocular surface. In addition, the predisposition of some patients to mucin balls indicate that as yet unknown patient characteristics are also involved in mucin ball aetiology [357–359, 363, 364].

**Prognosis**

Mucin balls are not embedded in the epithelium and are blinked away rapidly resolving in a matter of minutes. Mucin balls represent a disruption of the mucus phase of the tear film. Mucus prevents attachment of microorganisms to the corneal surface, it reduces friction and protects the ocular surface. Interestingly, the presence of mucin balls was found to be a protective indicator of corneal infiltrate development during silicone hydrogel lens wear [365]. Patients, which formed mucin balls, were found to have an 84% decreased hazard of corneal infiltrate development. It is thought that presence of mucin balls represents a more concentrated or viscous mucus layer, which prevents upregulation of the immune response against bacterial ligands [365, 366].

**Management**

- Optimise the lens fit, flat fitting lenses are thought to exacerbate mucin ball formation
- Advise the patient to use lubricating drops after waking up and before sleeping
- Suggest a shorter wearing schedule, daily wear rather than extended wear

**Figure 76:** Mucin Balls

## CONJUNCTIVAL COMPLICATIONS

### Conjunctival Redness

**Terminology [120]**

- Hyperaemia – Increased blood in a tissue, leading to engorgement or injection, causes redness of the affected tissue
- Engorgement – Excessive fullness of a vessel caused by accumulation of blood
- Erythema – Redness of the skin caused by congestion of the capillaries
- Injection – The act of forcing a liquid such as blood into a tissue

The term conjunctival redness is potentially confusing as it may not be clear if it refers to the bulbar, tarsal or limbal conjunctiva. It is also important to differentiate it from CLARE or contact lens acute red eye, which is associated with extended wear of contact lenses. CLARE is discussed in a later section of this chapter. In this section,

conjunctival redness refers to the bulbar conjunctiva. Tarsal and limbal redness are discussed in later sections. Due to the fact that conjunctival redness is so obvious and easily recognisable, it is often the only tissue reaction reported as a symptom by the patient. The causes of redness are numerous making it difficult to diagnose. Conjunctival redness is generally asymptomatic, but patients may complain of itching, congestion, a warm feeling and mild irritation. It is common with hydrogel lenses, especially when used with preservative based care systems and less common with RGP and silicone hydrogel lens wear.

**Aetiology [21, 367]**

- Local mechanical effect on the conjunctiva by the contact lens can lead to increased redness. Trauma is known to cause mast cell degranulation resulting in histamine release. Histamine causes vasodilation resulting in increased redness and swelling (chemosis)
- Metabolic influences – Vasodilation of the arterioles can be caused by hypoxia; hypercapnia, or acidic shift through the accumulation of lactic and carbonic acid; increased osmolarity; and due to repeated action potentials, which lead to a flood of potassium which cannot be effectively removed by the sodium-potassium pump
- Chemical influences – Non-toxic chemicals introduced into the eye by the insertion of a contact lens can lead to vasodilation of the arterioles, due to an acidic shift (due to different pH to that of the conjunctival tissue) and increased osmolarity when the solution is hypertonic
- Toxic reaction – Noxious preservatives, buffers, enzymes, chelating agents and other chemicals incorporated into contact lens care products can cause conjunctival redness
- Allergic reactions – Atopic individuals experience conjunctival redness that coincide with seasonal fluctuations in the concentration of airborne allergens. Deposits on lenses, as well as chemicals can also trigger allergic reactions
- Inflammation of the cornea, conjunctiva or other tissues will lead to conjunctival redness

**Management**

Treatment options fall into four broad categories depending of the cause of the conjunctival redness.

- Alterations to the lens type, design, material and modality of wear
- Alterations in care systems
- Improvement of ocular hygiene
- Medical treatment with topical drugs, such as vasoconstrictors

Resolution of contact lens-induced conjunctival redness is extremely rapid, taking minutes rather than days to recover to normal.

**Contact Lens Induced Papillary Conjunctivitis (CLPC) or Giant Papillary Conjunctivitis (GPC)**

CLPC or GPC is an inflammatory condition of the upper tarsal conjunctiva. The condition is characterised by mucus discharge, redness of the upper tarsal conjunctiva and the presence of polygonal to irregular papillae, which can be evenly distributed across the entire tarsus or localised to a few areas on the tarsus, usually corresponding to the corresponding edge of the contact lens, discomfort and contact lens intolerance. The condition was first reported by Dr. Tom Spring in 1974 and later Allansmith et al., 1977 coined the term GPC [368]. GPC implies very large papillae, which are not often seen with contact lens wear, but is more often associated with protruding nylon sutures, scleral buckles and elevated corneal deposits. In milder forms, this condition has been termed lid roughness and

papillary hypertrophy, and therefore a more appropriate term to use in contact lens wear is CLPC – contact lens induced papillary conjunctivitis. The aetiology includes:

- Mechanical trauma – leading to mast cell degranulation in the conjunctival epithelium and stroma, which leads to the release of histamine and other immune modulators. Chin, 2006 suggests that GPC is not an allergic reaction, but is really a reaction to irritation [369]. Donshik and Porazinski, 1999 suggest that GPC is the result of chronic irritation during the 8000 blinks per day, associated with contact lens edges, prosthesis or sutures. Hyperactivity of mast cells and immune cells promote collagen growth to form papillae. According to them, the levels of histamine, eosinophils and proteins are not elevated in GPC. GPC is more frequent with 4 week or longer replacement schedules (36% vs. 4.5%) [370]
- IgE mediated reaction or immediate hypersensitivity reaction (Type I) – Antibodies proliferate when the conjunctiva is exposed to certain antigens. A chain reaction is set in motion that leads to mast cell degranulation, release of inflammatory mediators and other substances that can affect tissue damage and repair. Patients with CLPC exhibit large numbers of degranulated mast cells in the epithelium and elevated levels of IgE in the tears [371]. The antigen thought to be responsible for the reaction is the deposits on the anterior surface of the lens
- Delayed hypersensitivity reaction (Type IV) – Due to the presence of large numbers of basophils in the conjunctival epithelium and substantia propia. Allansmith et al., 1977 suggested that CLPC has a delayed course and is mediated by sensitised T lymphocytes and antibodies. The antigens leading to the reaction is thought to be deposits on the anterior surface of the lens [368]
- Other causes include; lens material, solution toxicity, hypoxia and Meibomian gland dysfunction
- The pathophysiology of CLPC/GPC is complicated with both immune and mechanical mechanisms playing a role in the development of this condition. Understanding these mechanisms is important in both treatment and prevention of giant papillary conjunctivitis [372]

**Table 45:** Signs of CLPC [38]

| Clinical signs of CLPC | |
|---|---|
| **Feature** | **Signs** |
| Papillae<br>♦ Location<br>♦ Type<br>♦ Distribution | <br>Upper tarsal conjunctiva<br>Polygonal, hyperaemic, elevations ranging in size from 0.5 - >2 mm<br>Localised to a region corresponding to the lens edge on the tarsus or evenly distributed across the tarsus |
| Lid oedema | Not common |
| Bulbar/limbal redness | Not common but can be present in severe cases |
| Unilateral/bilateral | Unilateral or bilateral |

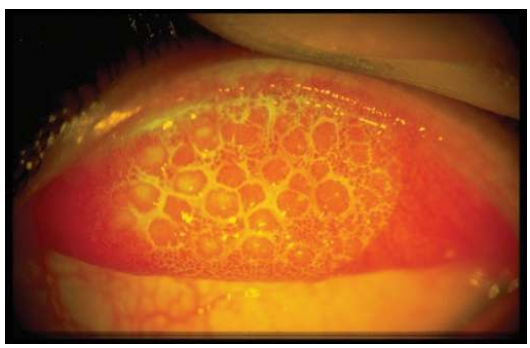

**Figure 77:** CLPC, note the giant papillae and mucus

**Stages According to Allansmith et al., 1977**

Stage 1 – Preclinical, characterised by minimal patient symptoms and no ocular signs

Stage 2 – Early clinical, characterised by mild symptoms and mild hyperaemia, as well as early papillae

Stage 3 – Moderate, characterised by moderate symptoms, hyperaemia and elevated papillae and moderate to severe coatings of mucus on the lens

Stage 4 – Severe, characterised by total lens intolerance and large or giant papillae.

**Management [21]**

- Reduce wearing tine or cease lens wear until inflammation subsides
- Increase frequency of lens replacements – daily replacement preferable
- Change lens material - Proclear Compatibles (Cooper Vision) or RGP lenses
- Improve solutions – hydrogen peroxide or preservative free systems
- Use protein removers and surfactant cleaners
- Improve ocular hygiene and treat MGD and blepharitis
- Use preservative free ocular lubricants
- Cold compresses may alleviate symptoms

Medical treatment according to the Wills Eye Manual – Use a topical mast cell stabiliser (Cromolyn sodium) or combination of mast cell stabiliser/antihistamine (Olopatadine) qid. In severe cases short term low-dose loteprednol (0.2–0.5%) or fluorometholone (0.1%) qid can be used [373]. According to Khurana et al., 2010 Olopatadine is effective in alleviating signs and symptoms of contact lens-induced mild to moderate papillary conjunctivitis and is comparable with Fluorometholone in efficacy [374]

The prognosis for CLPC after ceasing lens wear is good. Even in the most severe cases symptoms, tarsal redness and excessive mucus, disappear within weeks. The papillae take much longer to resolve, months rather than weeks. However, the condition can recur especially in atopic patients when the stimulus is reintroduced. The differential diagnosis includes conjunctival follicles, which are associated with viral or chlamydial conjunctival infections, and vernal conjunctivitis, which is not associated with contact lens wear.

## LIMBAL COMPLICATIONS

"Limbus" is the Latin word for border. Although the limbus appears as a distinct border when viewing the eye macroscopically, the limbus appears as a gradual transition zone (0.2–0.4 mm wide) between the cornea and conjunctiva, when viewed under magnification. The anatomy of the limbus is discussed in chapter 2. Histologically the limbus is much harder to define, various histological features that define the limbal region start and finish at different locations, some abrupt and some more gradual. However, a 1.5 mm zone encompasses all these features. Specific changes that take in the transition from the cornea to the limbus include the following [21]:

- Abrupt termination of Bowman's membrane
- Gradual thickening of the epithelium
- Introduction of loose connective tissue that underlies the conjunctival epithelium
- Increasing regularity of the anterior stromal lamellae
- Appearance of blood vessels in the stroma. The limbus is the region where the vascular network of the conjunctiva gives way to the avascularity of the cornea

Imbedded in the limbus is the capillary plexus, it is also the site of the corneal stem cells, which are the primary source for the differentiation and proliferation of the corneal epithelium and there is a pronounced flattening of the corneal surface to the conjunctival surface [5]. These three features; the capillary plexus, stem cells, and the limbal ridge; makes the limbus susceptible to metabolic, immunologic, toxic and physical insult, all of which can be caused by a contact lens. The integrity of the limbus is more likely to be compromised by soft lenses or scleral lenses, because of these lenses physical proximity to the tissues. Corneal RGP lenses only intermittently impinge on the limbus.

### Limbal Redness

Careful inspection of the limbus reveals the presence of anterior limbal loops, which can be two or three layers on top of one another as the limbal vascular plexus extends toward the cornea (Figure 78). Each successive loop becomes finer and the innermost loops are called the terminal arcades.

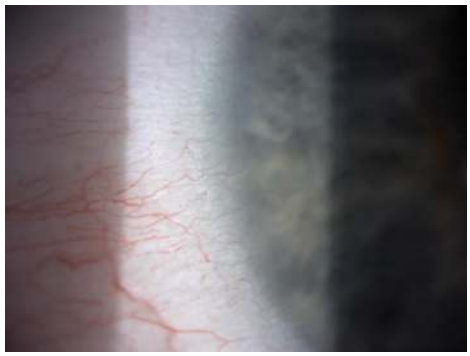

**Figure 78:** Normal vasculature of the limbal region

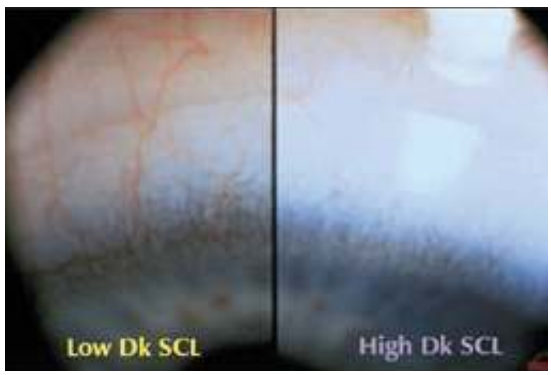


**Figure 79:** Limbal redness caused by low Dk/t lenses compared to appearance after wearing high Dk/t lenses in the same patient

When the limbus is physically or physiologically stressed, these vessels dilate making the vessels much more visible giving rise to limbal redness (Figure 79). Two types of vessels can be visualised with the slit lamp; a recurrent vessel, which appears as a single vessel with an accompanying shadow representing a single arteriole and its venule; and spike vessels, which looks similar to the recurrent vessels without the accompanying venules (shadows). The lumen of the arteriole can become so narrow that only clear serum and not even red blood cells can pass through.

Conventional hydrogel lens wear induces a marked increase in limbal redness during open-eye wear, which is not seen with silicone hydrogel lens wear or without lens wear (Figure 79). Silicone hydrogel lens wear, either with open or closed eyes, has a similar appearance to no lens wear. The development of limbal redness is not associated with any subjective symptoms. However, patients with severe complications and coincidental limbal redness will suffer from discomfort and pain.

**Aetiology**

- Hypoxia – Papas, 1998 demonstrated a strong inverse relationship between the oxygen transmissibility of contact lenses and limbal redness. The lower the Dk/t, the greater the limbal redness [36]. The mechanism by which hypoxia induces limbal redness is unclear, but Papas, 2003 proposed the following sequence of events. Hypoxia stimulate the vascular endothelium to release nitrous oxide or prostaglandins. These mediators diffuse toward the smooth muscle cells that compromise the pre-capillary sphincters, which relax resulting in increased blood flow to the hypoxic region [375]
- Infection – Infection of the cornea leads to a cascade of inflammatory events to cause limbal redness. Vasodilating agents, histamine, prostaglandins, and nitrous oxide are released increasing perfusion. This allows immune cells to approach the site of the infection. The limbal vessel walls increase in permeability and cells, as well as fluid, pass into the surrounding tissue leading to a milky haze surrounding the engorged limbal vessels [21]
- Inflammation – An increase in the inflammatory cell population occurs overnight in the conjunctival sac. Therefore, our eyes appear red upon awakening in the morning. Contact lenses can alter the concentrations of inflammatory mediators in the tear film, which may explain why patients who wear lenses on an extended wear basis, are more prone to contact lens acute red eye [47]
- Trauma – The constant physical presence of a contact lens on the limbal area may release inflammatory mediators, which result in limbal redness
- Solution toxicity or hypersensitivity – Solution preservatives may cause a delayed hypersensitivity reaction or act directly on the pre-capillary sphincters or the vessel walls, causing vessel distention and limbal redness [376]

**Management [21]**

Limbal redness in itself is harmless and does not cause discomfort for the lens wearer. However, it is an important sign of ocular distress and an indicator that action should be taken. The severity, extent and whether it is chronic or acute will often give clues to its cause. A useful strategy to use when examining patients with limbal redness would be to consider whether the limbal redness is acute, chronic, localised or circum-limbal.

- Acute local limbal redness is most probably due to keratitis near to the region of limbal redness. This requires aggressive treatment with anti-inflammatory and anti-infective drugs
- Chronic local limbal redness is most probably due to a defect in the edge of an RGP or soft lens and should be easily dealt with
- Acute circum-limbal redness is most likely due to a solution immediate hypersensitivity or toxic reaction and the solutions should be changed
- Chronic circum-limbal redness is most likely the result of chronic hypoxia induced by a contact lens which requires replacement with a high Dk/t lens

**Prognosis and Differential Diagnosis [21]**

Recovery once the causative agent is removed is rapid and limbal redness will generally completely resolve within 2–7 days.

Differential diagnosis includes:

- Corneal neovascularisation
- Pannus
- Contact lens-induced superior limbic keratoconjunctivitis
- Prominent palisades of Vogt which may appear like a prominent plexus of limbal vessels

## VASCULARISED LIMBAL KERATITIS (VLK)

Vascularised limbal keratitis (VLK) is a complication of corneal RGP lens wear (both medium and high gas permeable materials). It is characterised by an inflammation of the limbus in association with a process of vascularisation in the 3 and 9 o'clock cornea positions (Figure 80). VLK typically develops over a period of 6–24 months. It can be graded according to severity into four stages, stage 1 being the least severe [352].

Stage 1 – Epithelium adjacent to the limbus appears disrupted and punctate staining is evident. An elevated whitish opaque mass of hyperplastic corneal and limbal epithelial tissue can be observed at the 3 and 9 o'clock corneal locations with ill-defined borders. The mass appears to bridge from the conjunctiva across the limbus onto the cornea and the tear film meniscus is absent or disrupted. The patient typically experiences no symptoms

Stage 2 – This stage is characterised by symptoms, such as mild discomfort, lens intolerance and conjunctival redness. Corneal infiltrates may be present, and staining is more severe

Stage 3 – Symptoms of discomfort, reduced wearing time, conjunctival and corneal staining, and conjunctival hyperaemia, as well as a more significant infiltrative response are evident. The limbus and conjunctiva may appear to be oedematous and it is not uncommon to see a vascular leash emanating from the conjunctiva encroaching upon the hyperplastic mass

Stage 4 – This stage is characterised by severe discomfort and photophobia, as well as pain when the lens edge impinges on the hyperplastic mass and wearing lenses become intolerable. Significant conjunctival hyperaemia and staining are present, often associated with erosion of the elevated hyperplastic mass. Superficial and deep vascularisation is common

### Aetiology

The aetiology is unknown, but Grohe and Lebow, 1989 hypothesised that VLK is caused by an interruption of the normal tear film dynamics at the limbus, caused by the corneal RGP lenses. Constant ongoing physical irritation of the poorly lubricated ocular surface by the RGP lens and lids induces inflammation, which progress to the stages of VLK if left untreated. VLK is can therefore be seen as a more severe form or at least the result of 3 and 9 o'clock staining caused by corneal RGP lenses [352].

### Management [21]

Management depends on the severity of the condition. At the very least the lens design should be altered, wearing schedule adjusted, lubricating drops prescribed and punctal plugs considered. In the more severe cases, lens wear should be suspended, and medical treatment instituted. Corticosteroid antibiotic combinations should be considered if the inflammatory response is severe. Soft or scleral lenses may be considered after the inflammation has resolved to avoid a repeat episode.

### Prognosis and Differential Diagnosis

The prognosis for recovery of VLK is generally very good and even severe cases can recover within a few weeks with appropriate treatment. However, if lens wear recommences prematurely, a rebound can occur whereby the condition flares up and progresses rapidly to the previous (more severe) stage.

The differential diagnosis includes; Phlyctenulosis, peripheral corneal ulceration, pterygium, pannus and pinquecula.

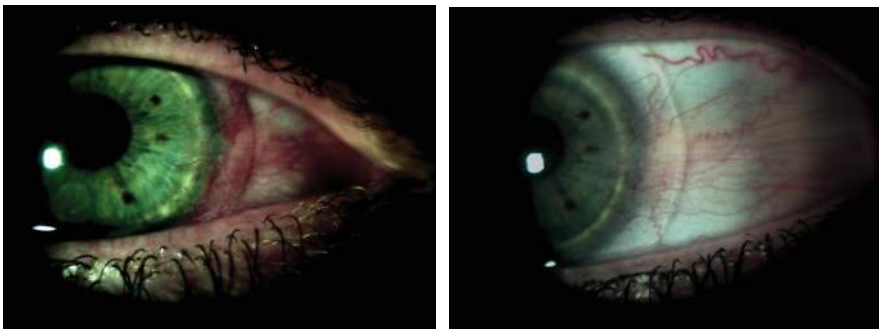

**Figure 80:** VLK in a keratoconic patient due to RGP corneal lens wear.

These photographs illustrate the effect of treatment using a combination of topical steroids and refitting with a bespoke soft contact lens. The left photograph was taken at the start of therapy and the right two weeks later.

## CONTACT LENS INDUCED SUPERIOR LIMBIC KERATOCONJUNCTIVITIS (CLSLK) [21]

This syndrome compromises of a combination of tissue pathologies. The tissues affected, include the corneal epithelium and stroma, the limbus and the bulbar, as well as the tarsal conjunctiva (Figure 81). CLSLK is associated with the use of thimerosal-based contact lens solutions, mechanical effects of the contact lens edge due to excessive lens movement, lens deposits and biofilms, and possibly hypoxia below the superior lid. A similar condition – Theodore's SLK – is found in non-contact lens wearers (may also be found in contact lens wearers), which is linked to thyroid disease [9]. In the days of thimerosal solutions, the prevalence was estimated to be around 6.5%, but with modern disinfecting solutions the prevalence is much lower. Symptoms include increased lens awareness, loss of lens tolerance, foreign body sensation, burning, itching, photophobia, redness and increased lacrimation. Signs include thickening, inflammation and radial injection of the bulbar conjunctiva below the superior lid, especially at the limbus. Fine papillae on the superior palpebral conjunctiva, fine punctate staining of the superior cornea, conjunctiva and limbus, as well as micro-pannus with filaments may be present. The condition is usually bilateral, but not symmetrical. Management includes cessation of lens wear, changes in solutions, aggressive lubrication, punctal occlusion, treatment of concurrent blepharitis and in severe cases the application of silver nitrate. Topical steroids and immunosuppressive drugs, such as cyclosporine may also be useful in certain cases [373]. The prognosis is good, but recovery is slow with resolution within 3 weeks to 9 months after cessation of lens wear.

**Table 46:** Differences between Theodores SLK and CLSLK [21]

| Feature | Theodore's SLK | CLSLK |
|---|---|---|
| **Age** | >40 years | <40 years |
| | Theodore's SLK | Contact lens induced superior limbic keratoconjunctivitis (CLSLK) |
| **Gender** | >females | Equal male: female |
| **Age** | Middle aged >40 years | Younger <40 years |
| **Associated factors** | Linked to thyroid disease | Soft contact lens wear<br>Increases lens movement<br>Soiled lenses<br>Thimerosal lens solutions |
| **Symptoms** | Mild to severe irritation without lenses<br>Vision rarely effected | Mild to severe irritation with lenses<br>Vision can be reduced |

| Feature | Theodore's SLK | CLSLK |
|---|---|---|
| **Signs** | Mild superior corneal staining<br>Superior bulbar conjunctival redness & chemosis<br>Limbal redness<br>Grade 3 papillary hypertrophy<br>Corneal filaments | Severe superior corneal staining<br>Superior bulbar conjunctival redness & chemosis<br>Limbal redness<br>Grade 1 papillary hypertrophy |
| **Staining** | Superior corneal NAFL staining | Superior corneal Rose Bengal or Lissamine Green staining |
| **Pathology** | Epithelial keratinisation and nuclear degeneration | Epithelial keratinisation, neutrophilic response, reduced number of goblet cells |
| **Management** | Lubricants, silver nitrate application, bandage lens therapy, pressure patching, conjunctival resection, conjunctival cauterisation | Temporary cessation of lens wear, interim corticosteroids, prostaglandin inhibitors and lubricants, change lens design and solutions, regular lens replacement or daily disposables |

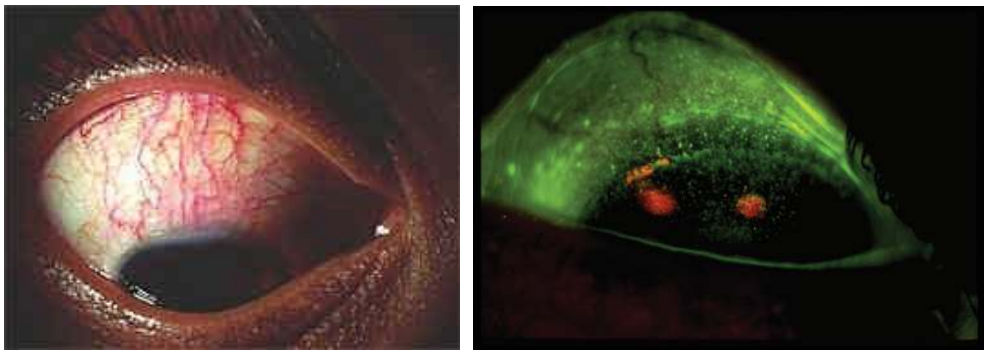

**Figure 81:** Theodores SLK note the hyperaemia and characteristic NAFL staining of the superior bulbar conjunctiva

## CORNEAL COMPLICATIONS

### Corneal Oedema

Corneal oedema induced by contact lenses was first recognised by Adolf Fick in 1888. He noted that the cornea became cloudy within hours of insertion of a glass haptic lens, but more impressively also noted that the onset of the clouding could be delayed by trapping an air bubble beneath the lens. In 1889 August Müller correctly identified that the clouding was caused by lack of tear exchange beneath the lens. Oedema refers to an increase of the fluid content of a tissue [294]. Corneal swelling results in an increase in the thickness of the cornea, therefore corneal oedema is usually expressed as the percentage increase in thickness. An increase of 55 μm would equate to ±10% increase in thickness [21].

Although it is typically the corneal stroma that swells, the corneal epithelium can also become oedematous. Different mechanisms are involved with epithelial swelling, usually caused by osmotic stress and stromal swelling by hypoxia.

Essentially ***all*** contact lenses, including silicone hydrogel lenses, induce some level of oedema related to the extent of corneal hypoxia induced by the lens. The oedema response of the cornea is not uniform due to:

- Variations in thickness across powered contact lenses
- Resistance of the peripheral cornea to swelling, due to limbal vasculature

**Epithelial Oedema**

A small number of vacuoles and bullae can sometimes be observed in the corneas of contact lens wearers. Although these vacuoles and bullae appear innocuous they need to be distinguished from small epithelial inclusions, which may be potentially serious [346]. It is important to note that epithelial oedema does not occur in response to contact lens induced hypoxia. The aetiology of epithelial oedema is two-fold; first, trauma can cause epithelial cells loss compromising the fluid barrier (zonula occludens) allowing fluid to enter the corneal epithelial layers; secondly, epithelial oedema follows hypotonic ocular exposure which inhibits the fluid barrier. Hypotonicity occurs with reflex tearing, RGP lens adaptation and environmental exposure (wind and low humidity) [21, 89, 377]. Sattler's veil refers to a diffraction phenomenon arising in the corneal epithelium due to oedema. The extra cellular space increases and is filled with fluid, which has a lower refractive index than the cells creating light scatter. This leads to halos and coronas being seen around lights [378] (Figure 82). Cox and Holden, 1990 found a strong positive relationship between relative halo brightness, degree of epithelial oedema, and contrast sensitivity loss. It appears that vision loss with physiologically induced levels of corneal oedema is primarily epithelial in origin, with stromal thickness increases up to 10% having little effect on vision. This indicates that the measurement of vision loss is not a good quantitative predictor of the presence or magnitude of physiological corneal oedema [379].

**Figure 82:** Sattler's veil

**Vacuoles**

Vacuoles can be observed in up to 10% of the normal non-lens-wearing population. The prevalence of vacuoles is related to lens material. Up to 32% prevalence occurs with low Dk/t thick extended wear hydrogel lenses. Vacuoles appear to be small spherical bodies within the corneal epithelium (5–30 μm in diameter). When viewed using indirect illumination, against the dark back ground of the pupil, they display unreversed illumination - distribution of light in vacuole is the same as the back ground. This is an important feature, which distinguishes vacuoles from microcysts. Vacuoles are more commonly seen toward the periphery of the cornea and seldom number more than 10. The fact that vacuoles display unreversed illumination suggests that their contents are probably gaseous and have a lower refractive index than the surrounding tissue. Vacuoles do not cause vision loss. Vacuoles indicate hypotonic stress rather than hypoxia and are therefore common, especially, if excess tearing occurs in the adaptation phase of RGP wear due to initial discomfort. They often disappear without intervention [380].

**Bullae**

Bullae are larger (>40 μm) than vacuoles and occur sub-epithelial. They are irregular in shape (oval) have indistinct edges. They appear flattened, pebble-like, can occur as single entities, or coalesce into clusters that contain many distinct elements. Bullae display reversed illumination or unreversed illumination depending on the refractive index of their contents (Figure 83). However, due to their indistinct edges this refractive index difference is not as pronounced as in vacuoles indicating that bullae may contain fluid rather than gas. Bullae may indicate chronic corneal epithelial oedema and needs to be managed [380].

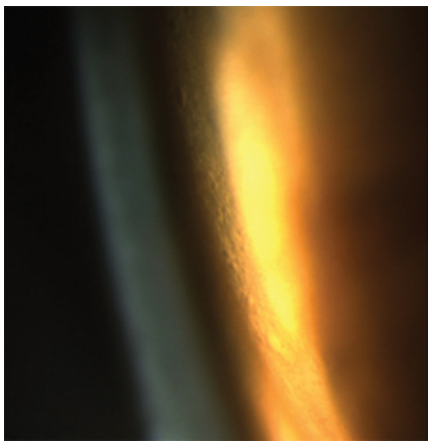

**Figure 83:** Epithelial bullae

**Epithelial Microcysts**

The first report of microcysts associated with contact lens wear was made by Ruben et al., 1976 and this observation was later confirmed by Zantos and Holden in 1978 [346, 381]. Epithelial microcysts can be readily observed with the slit-lamp and they are considered an important indicator of chronic metabolic stress in response to contact lens wear. Microcysts form as a direct effect of chronic hypoxia and acidosis resulting in altered cellular growth patterns [382]. Microcysts are typically 5–30 μm in diameter and have a uniform spherical or ovoid shape [380]. They appear as scattered opaque grey dots with focal illumination and as transparent refractile inclusions with indirect retro-illumination, usually after 1 week of extended wear, increasing in number and severity as extended wear continues (Figure 84). They display reversed illumination, indicating that the refractive index of the microcyst is higher than that of the surrounding tissue [380]. Compared to extended wear of hydrogel lenses, lower prevalence is associated with daily wear hydrogel lenses. Prevalence is nearly 100% with all extended wear hydrogel and low Dk/t RGP lenses and zero with silicone hydrogel lenses [21].

Bergmanson, 1987 postulates that the microcysts represent an extracellular accumulation of broken down cellular material trapped in the basal layers of the epithelium [383]. In a process similar to Cogan's microcystic dystrophy, the epithelial basement membrane folds and replicates to form intra-epithelial sheets that detach from the basement membrane and encapsulate the cellular debris. Madigan suggested that rather than an accumulation of extracellular debris, microcyst represent apoptotic dead cells, which either become phagocytosed by living neighbouring cells or remain involuted in intercellular spaces.

Currently, it is postulated that the microcysts form at the deepest level of the epithelium, where they are partially formed and difficult to observe. They then migrate to the surface of the epithelium, which is constantly growing in an anterior direction. Here they are more readily observed. They eventually break through the surface and leave minute pits that stain with NAFL [21].

Vision is generally unaffected, and patients are unaware of microcysts except in extreme reactions, where they may have a mild anterior uveitis accompanying the reaction. Epithelial microcysts are managed according to their severity. If the reaction is less than grade 2, no action is usually required, and the patient is monitored carefully. If the reaction is grade 3 and higher extended wear should be immediately stopped, and lens wear discontinued for at least 1 month until the cornea clears. When refitting the patient, daily wear should be recommended in high Dk/t soft and RGP materials. It is also important to remember that reverse geometry lenses used in orthokeratology induce microcysts within 3 months of wear, therefore these patients need careful follow-up and if microcysts occur reverse geometry lens designs should be avoided [21, 382].

Finally, clinicians should be aware that ceasing contact lens wear may not have an immediate improvement in the microcystic reaction. In fact, the amount of microcysts may increase when the epithelial metabolism normalises before decreasing. This is due to the accelerated growth and mitosis leading to accelerated removal of cellular debris and rapid movement of microcysts to the surface. Numbers of microcysts gradually decrease until they are eliminated [380, 384].

**Figure 84:** Epithelial microcysts

**Epithelial Wrinkling**

Epithelial wrinkling is a severe complication of contact lens wear and is characterised by the appearance of a series of deep parallel grooves in the corneal surface – wrinkled effect (Figure 85). Lowe and Brennan, 1987 postulate that the wrinkling involves the epithelium and anterior stroma and it is interesting to observe that in all reported cases of epithelial wrinkling the lens parameters were remarkably similar:

- Highly elastic hydrogel materials
- Custom designs
- Extremely thin
- Mid water content (50–55%)
- Steep fitting

Lowe and Brennan propose that the excessive elastic force draws the corneal tissue inwards from the limbus, causing the wrinkled appearance [385]. Bruce and Brennan, 1990 also postulated an osmotic aetiology [386]. Finally, Epstein (in Speciality contact lenses, a fitters' guide), 1996 suggested that epithelial oedema is the cause. According to him, swelling pushes the cornea up against the lens so that it folds back on itself causing the wrinkles.

Vision loss can be dramatic and proportional to the degree of distortion. Wrinkling is also extremely painful. The condition is managed by ceasing lens wear after which vision should return to normal within 24 hours. The patient can then be refitted with a more appropriate design devoid of inherent elastic forces.

**Figure 85:** Epithelial wrinkling

Epithelial wrinkling does not occur with RGP lenses, but Fischer-Schweitzer polygonal mosaics can occur with RGP extended wear lenses or aggressive rubbing of the eyes through closed lids. The pattern can be localised or cover the whole corneal surface, appearing as minute branching lines or furrows in the epithelial surface, that are revealed with NAFL (Figure 86). It is thought to be caused by wrinkling of Bowman's membrane during physical deformation of the cornea [387, 388]. The Fischer-Schweitzer mosaics, disappears within 10 minutes of removing the lenses and is asymptomatic. Treatment consists of altering the fit to relieve the pressure on the cornea.

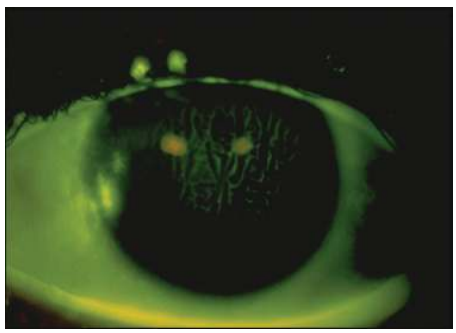

**Figure 86:** Fischer-Schweitzer polygonal mosaic

**Epithelial Staining**

Fluorescein was first used to examine the integrity of the cornea by Pflüger in 1882. This was just six years before the first contact lenses were fitted by Fick. However, it is only since the 1970s that fluorescein has been used routinely by clinicians when fitting contact lenses. Although corneal epithelial staining is not a "condition" in-itself, it represents tissue disruption and other pathophysiological changes of the cornea and the anterior eye. Fluorescein and the other vital dyes properties and uses are fully discussed in chapter 3 and should be reviewed. Unless otherwise stated, corneal staining refers to staining with fluorescein (NAFL) in this chapter.

Clinicians use the term "corneal staining" to describe bright areas of fluorescence in the corneal epithelium, after the instillation of NAFL dye and illumination with cobalt blue light (a yellow Wratten # 12 filter can be used to enhance the appearance). Corneal staining is common even in non-contact lens wearers. The most prevalent location of staining was the inferior region of the cornea followed by the nasal region of the cornea and the grade was typically 0.5–0.6 [389], This staining is typically associated with a poor quality tear film. In contact lens wearers, the prevalence of corneal staining is much higher, but the grade is typically low (0.50) and clinically insignificant. The areas of the cornea affected are typically the superior and inferior cornea and is associated with a rapidly destabilising pre-lens tear film (PLTF) and a thinning lipid layer, more in the vertical quadrants than in the horizontal quadrants. The PLTF is thinnest and most unstable at the tear prism margin border, hence least efficacious at preventing evaporation. Corneal staining may therefore be due, at least partly, to

excessive evaporation at the contact lens front surface [51, 390]. The prevalence of clinically significant staining (> grade 2) was 0.9% in soft lenses, 0.5% in RGP lenses, and 1.3% in PMMA lenses [391]. Visual acuity is generally unaffected by staining except in severe cases. Comfort depends on the severity of the staining, as well as the underlying cause. For example, staining caused by microbial keratitis can be extremely uncomfortable and the patient will also be photophobic.

**Corneal Staining can be Classified as [21, 89, 367]:**

- Punctate staining (Figure 87) – small superficial discrete dots are observed on the corneal surface. Also referred to as superficial punctate keratitis or erosion (SPK or SPE)
- Diffuse staining – Vast array of closely separated punctate spots gives rise to a diffuse appearance
- Coalescent staining – The constituent elements of staining are obscured giving an appearance of confluent or coalescent staining

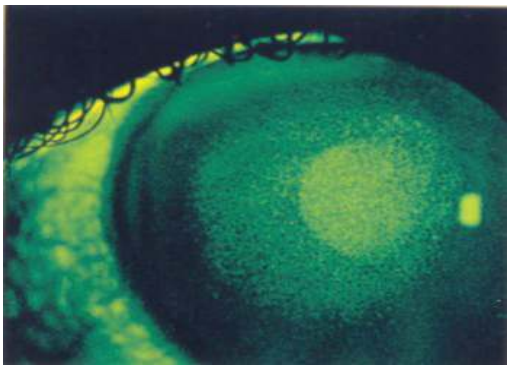

**Figure 87:** Severe central punctate staining

- 3 and 9 o'clock staining (Figure 88) – Classic form of staining seen in rigid lens wear and refers to triangular areas of staining at the nasal and temporal cornea outside the lens periphery. The apex of the triangle is typically away from the central cornea. It occurs primarily as a result of corneal non-wetting caused by the lids being bridged away from the cornea by the lens edge [392]

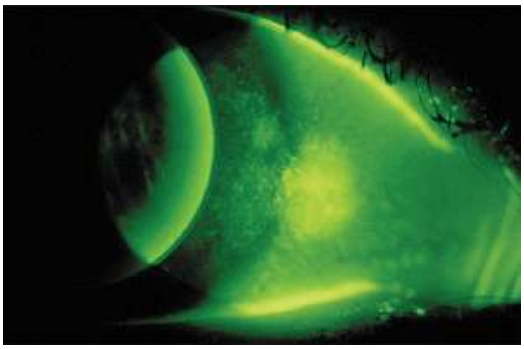

**Figure 88:** 3 and 9 o'clock staining

- Dimple veil staining (Figure 89) – This is not true staining but rather caused by NAFL pooling in indentations in the corneal left by bubbles that become trapped between a contact lens and the cornea. It is usually the result of poorly fitting lenses and occur centrally in steep fitting lenses and peripherally in high riding lenses fitted on with-the-rule corneal astigmatism [393]

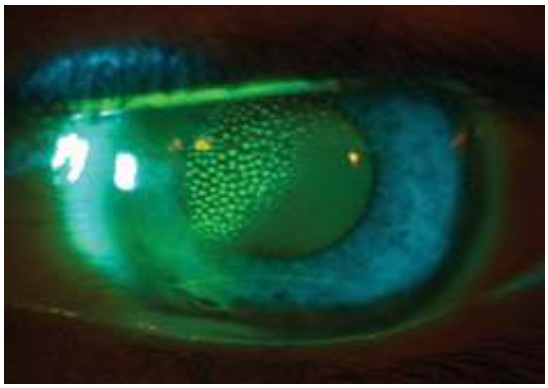

**Figure 89:** Dimple veil "staining"

- Inferior arcuate staining or smile staining (Figure 90) – This occurs on the inferior cornea between 4 and 8 o'clock, usually in soft contact lens wearers. It is believed that the aetiology includes a combination of factors, such as an insufficient post lens tear film, lens adherence and or lens dehydration [394]

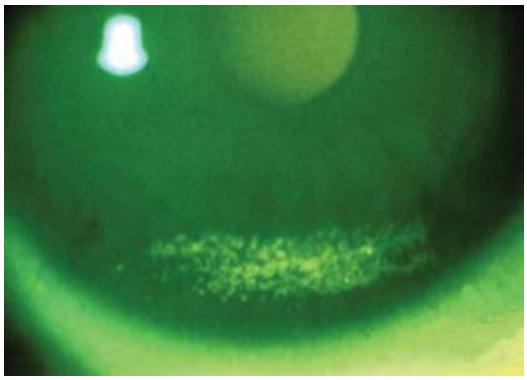

**Figure 90:** Inferior arcuate staining

- Superior epithelial arcuate staining (SEALs) (Figure 91) – Infrequent, asymptomatic complication of conventional soft lens wear. This is usually a full thickness lesion of the epithelium, in the area of the cornea covered by the superior lid. Usually within 2–3 mm from the limbus in the 10 to 2 o'clock region. It is also referred to as epithelial splitting and its aetiology is multifactorial. Mechanical chafing, as a result of the upper lid resting on the lens, resulting in excessive frictional pressure and abrasive shear forces on the corneal epithelial surface. Higher modulus lens materials, such as silicone hydrogels can contribute to the formation of SEAL's [395]

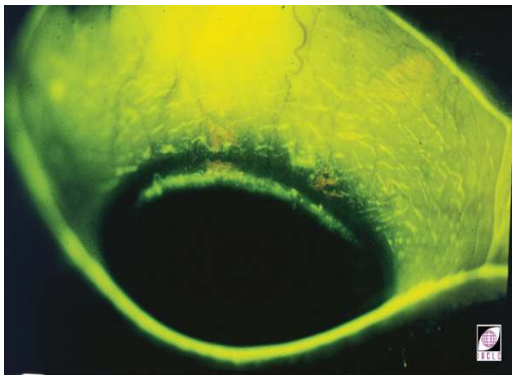

**Figure 91:** SEALS

- Epithelial plug (Figure 92) – This is a large discrete area, typically round in shape, of full thickness epithelial loss. This is usually caused by severe corneal metabolic compromise due to prolonged lens induced hypoxia. Many changes occur in the corneal epithelium, due to contact lens wear. These changes include; decrease in the number of cell layers; appearance of cuboidal rather than columnar basal cell shapes; and a reduction in the number of hemidesmosomes, which is the cause of epithelial plug formation [396]

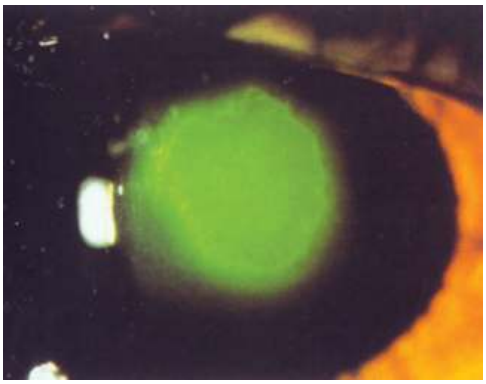

**Figure 92:** Epithelial plug

- Other types of staining include foreign body stains, abrasions and infectious staining

**Aetiology of Epithelial Staining [21, 87, 367]**

The causes of epithelial staining can be broadly classified into six aetiological categories:

- Mechanical – Sources of mechanical staining include lens defects, lens binding, lens bearing, foreign body trapped under the lens, and abrasions
- Exposure – In soft lens wearers this is inferior smile staining, SEALs and in RGP lens wearers 3 and 9 o'clock staining
- Metabolic – Staining induced by hypoxia caused by lens wear. This staining is generally diffuse, bilateral and encompasses most of the cornea. Microcysts can break through to the surface of the epithelium and result is fine punctate staining
- Toxic – Caused by preservatives in contact lens solutions. The staining is usually fine and diffuse covering most of the cornea
- Allergic – Fine diffuse staining covering most of the cornea in association with type 1 and type 4 hypersensitivity reactions
- Infectious – Epithelial staining overlies a corneal infiltrate and represents an overlying epithelial defect - ulcer

**Management**

The cause of the epithelial staining can often be identified from the patient history, type of lenses worn, lens care system used, inspection of the lens, and analysis of the form of staining. Clinical intervention is usually not required if the level of staining is less than grade 2. If staining is > grade 2 lens wear should be ceased until the staining resolves. Medical therapy in the form of topical antibiotics may be required to prevent secondary infection.

**Corneal Abrasions**

Corneal abrasions are also a form of epithelial staining. Abrasions are normally caused by mechanical injury, such as lens edges, finger nails or poorly fitting lenses. In keratoconus, corneal abrasions are quite common due to the

fragility of the corneal epithelium and flat fitting RGP lenses [397]. Abrasions, due to flat fitting RGP lenses can sometimes have a "swirl type" appearance and is referred to as "hurricane staining". According to the Wills Eye Manual a contact lens related abrasion and diffuse punctate keratitis, should be treated with a topical antibiotic with good gram-negative coverage, due to the increased risk of *Pseudomonas* infection. *Pseudomonas* readily adhere to biofilms on contact lenses [103, 109]) and cause microbial keratitis. It is also for this reason that contact lens wearers with abrasions should never be pressure patched. Fluoroquinolones and tobramycin antibiotics are good choices for treating contact lens related abrasions. Cycloplegia can also be used in more severe cases to reduce pain and inflammation. Steroids are not indicated [398].

**Stromal Oedema**

Contact lenses restrict the amount of oxygen available to the corneal epithelium, causing a hypoxic environment. The corneal epithelium then begins anaerobic respiration to produce energy, which leads to excess lactate production. The lactate then moves into the corneal stroma, which is osmotically balanced by the influx of water into the stroma. The endothelial ion pump-mechanism is overwhelmed, which results in corneal oedema and loss of transparency [5, 20].

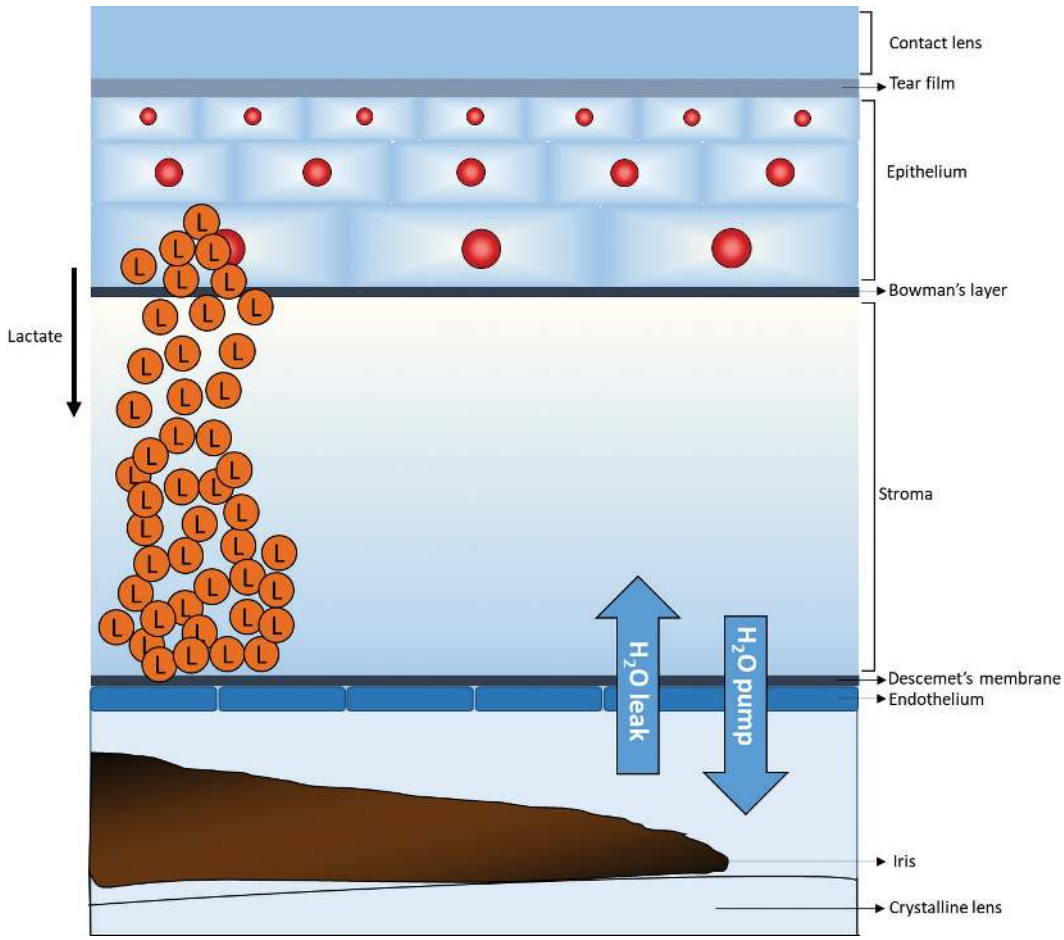


**Figure 93:** Pump-leak hypothesis of corneal oedema

The pump-leak hypothesis simply states that the passive natural leakage of fluid into the stroma driven by imbibition pressure is counteracted by an active bicarbonate-and $CO_2$-dependent endothelial pump. This pump works by transporting bicarbonate in the stroma toward the aqueous, both across the apical membrane of the endothelial cells and into the para-cellular spaces. Water passively follows the bicarbonate transport maintain corneal hydration.

**Central Corneal Clouding**

Corneal oedema associated with tight fitting PMMA lenses is known as central corneal clouding (CCC). PMMA has no oxygen transmissibility and coupled with the poor tear exchange associated with tight lenses, a hypoxic state is created. This results in a round area of clouding under the lens in the central cornea (Figure 94). CCC indicates a gross level of oedema, which is rarely observed with modern contact lenses and materials [21]. More subtle signs of oedema can be seen with careful slit lamp examination of the cornea and include, striae, folds and haze.

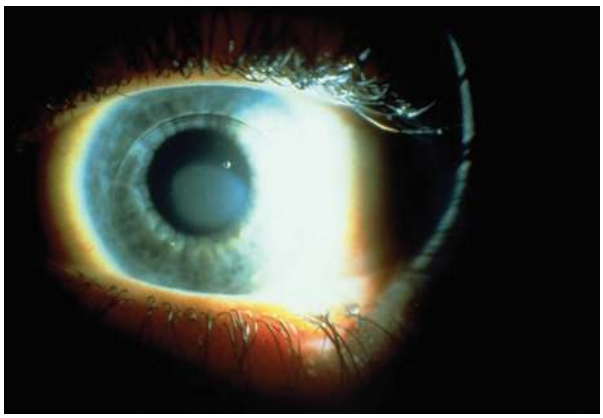

**Figure 94:** Central corneal clouding (CCC)

**Striae**

Striae appear as fine wispy, white vertically oriented lines in the posterior stroma using direct focal illumination (Figure 95). You can also visualise them as dark lines in the red fundus, reflex using retro illumination. Striae are present when oedema reaches at least 5% and they do not cause vision loss. Striae represent fluid separation of the predominantly vertically oriented collagen fibres in the posterior stroma [21, 399].

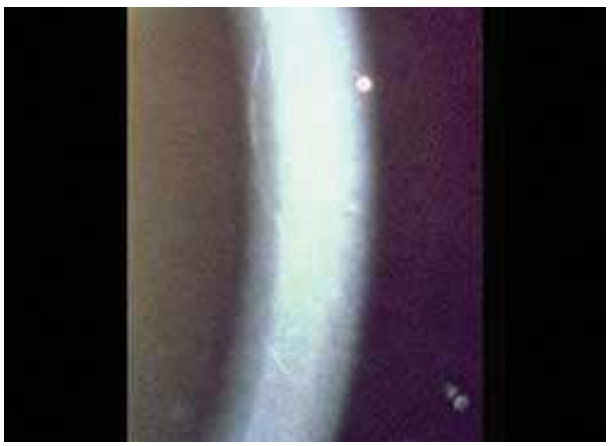

**Figure 95:** Striae, folds and cornea haze due to stromal oedema

**Folds**

Folds can be observed in the epithelial mosaic as compressed grooves or raised ridges or as areas of buckling when the level of oedema ≥ 8%, Folds are best observed using specular reflection. Folds are caused by physical buckling of the posterior stromal layers in response to high levels of oedema [21, 399].

**Haze**

At about 15% oedema the stroma takes on a milky appearance due to the loss of transparency. The haze appears as a fine grey haze against the dark background of the pupil using indirect illumination. Sclerotic scatter enhances the clinical picture. Stromal haze can affect vision, especially if the oedema exceeds 20%. Haze is a more advanced form of striae with gross separation of collagen fibres throughout the full thickness of the stroma. This causes failure of the optical coherence of the stromal lamellar layers, reducing transparency [21, 399].

**Management of Stromal Oedema [21]**

- Increase Dk/t of the RGP lens material
- Reduce the RGP lens thickness
- Address RGP lens fit, use flatter base curve, increase the edge lift, reduce lens diameter, and or add a fenestration to the lens
- With soft lenses change from hydrogel to silicone hydrogel material, or from daily wear to disposable monthly or daily disposable lenses
- Reduce wearing time (no extended wear), postpone or abandon lens wear

## STROMAL THINNING

Corneal oedema is a reliable indicator of the level of hypoxic stress induced by contact lens wear. It is an acute response and oedema increases at a steady rate within hours of lens wear. Conversely, the oedema decreases within a few hours of removing the hypoxic stress (in this case the contact lens). Stromal thinning is an insidious chronic change often masked by oedema [400–402]. The stroma thins around 2.1–2.6 μm per year in long term contact lens wear. It is more common in low Dk/t daily wear rigid and extended wear hydrogel lenses. The causes of stromal thinning are thought to relate to the disruption and loss of keratocytes, which synthesise and maintain the collagen and extracellular matrix of the stroma. Confocal microscopy has confirmed the loss of keratocytes in contact lens wear. Anterior keratocyte density in a non-contact lens wearing population was 925 ± 276 cells/mm$^2$ and in patients wearing daily wear hydrogel lenses this decreased to 757 ± 243 cells/mm$^2$ [403, 404]. Care must be taken to interpret the results of the confocal microscopy studies. Stromal oedema results in the keratocytes being distributed further apart and therefore an underestimation of the keratocyte density.

Holden et al., 1985 proposed two possible mechanisms. Firstly, stromal keratocytes may lose their ability to synthesise new stromal tissue through the effects of lens induced tissue hypoxia, and/or the indirect effects of chronic lens induced tissue acidosis caused by an accumulation of lactic and carbonic acid. Secondly, constantly elevated levels of lactic acid associated with chronic lens induced oedema may lead to some dissolution of the mucopolysaccharide ground substance of the stroma [400]. Jalbert and Stapleton, 1999 attributed keratocyte loss in contact lens wear to three possible aetiologies; hypoxia, cytokine-mediated effects and mechanically induced effects [399, 405].

### Management

Contact lens wear should be ceased and more appropriate materials, lens designs and wearing modalities implemented. Stromal thinning may be associated with structural weakening of the cornea, which may lead to greater susceptibility to corneal warpage induced by contact lenses. Stromal thinning in long term contact lens wear also have implications for refractive surgery and may preclude these patients from the procedure. Stromal thickness recovers very slowly after lens wear stops (months to years) and its effects are long lasting.

## DEEP STROMAL OPACITIES OR CONTACT LENS ASSOCIATED DEEP STROMAL OPACITIES (CLADSO)

Descriptions of CLADSO vary considerably and can present as whitish dots directly anterior to Descemet's membrane (cloudy dystrophy) in the stroma. Stellate folds may also be visible in Descemet's membrane, and mild polymegathism of the endothelial cells is also seen. CLADSO occurs with low Dk/t HEMA and PMMA lenses. Vision loss is variable, and patients complain of discomfort as well as photophobia. The exact cause of CLADSO is not known. However, a variety of aetiological factors have been suggested [399, 406–409]:

- Long-term contact lens wear
- Exposure to heavy metals
- Allergic reaction to thimerosal
- Exposure to chlorhexidine
- Chronic hypoxia
- Chronic hypercapnia
- Endothelial dysfunction
- Suction effects by the lens

### Management

Early recognition is vital. Patients can then be refitted with high Dk/t lenses of different design (RGP) after lens cessation has resolved the CLADSO. Thimerosal and chlorhexidine is no longer used in contact lens cleaning products. The prognosis is protracted and the opacities may need up to 12 months to resolve leading to permanent visual impairment [21].

### Microdot Deposits

Confocal microscopy of contact lens wearers has revealed the presence of features presumed to be of a pathologic nature. Microdots appear as numerous white dots in the stroma and are presumed to be associated with chronic hypoxia and stromal keratocyte apoptosis. They are more common in soft lens wear than rigid lens wear. Microdots are presumed to be a precursor of CLADSO. Microdots can also be observed in normal non-lens wearing corneas so more research is needed to clarify their significance [364, 399, 410, 411].

## CORNEAL NEOVASCULARISATION(CNV)

Corneal neovascularisation refers to the presence of blood vessels in the normally clear avascular cornea. CNV is caused by infection, inflammation, trauma and degenerative conditions (Table 45). This discussion will pertain to CNV due to contact lens wear.

**Table 47:** Clinical conditions that induce corneal neovascularisation [412]

| Clinical conditions that induce corneal neovascularisation. |
|---|
| ***Infectious*** |
| Herpes simplex keratitis<br>Herpes zoster keratitis<br>Syphilis<br>*Pseudomonas*<br>*Chlamydia trachomatis*<br>*Candidiasis*<br>*Fusarium*<br>Aspergillosis<br>Onchocerciasis |

| *Inflammatory* |
|---|
| Stevens–Johnson syndrome<br>Acne rosacea<br>Graft rejection<br>Graft-versus-host disease<br>Pemphigoid<br>Atopic conjunctivitis<br>Dry eye |
| ***Trauma*** |
| Contact lens wear<br>Alkali burns<br>Ulceration<br>Mechanical |
| ***Degenerative*** |
| Terriens marginal degeneration<br>Pterygium<br>Aniridia<br>Limbal stem cell deficiency |

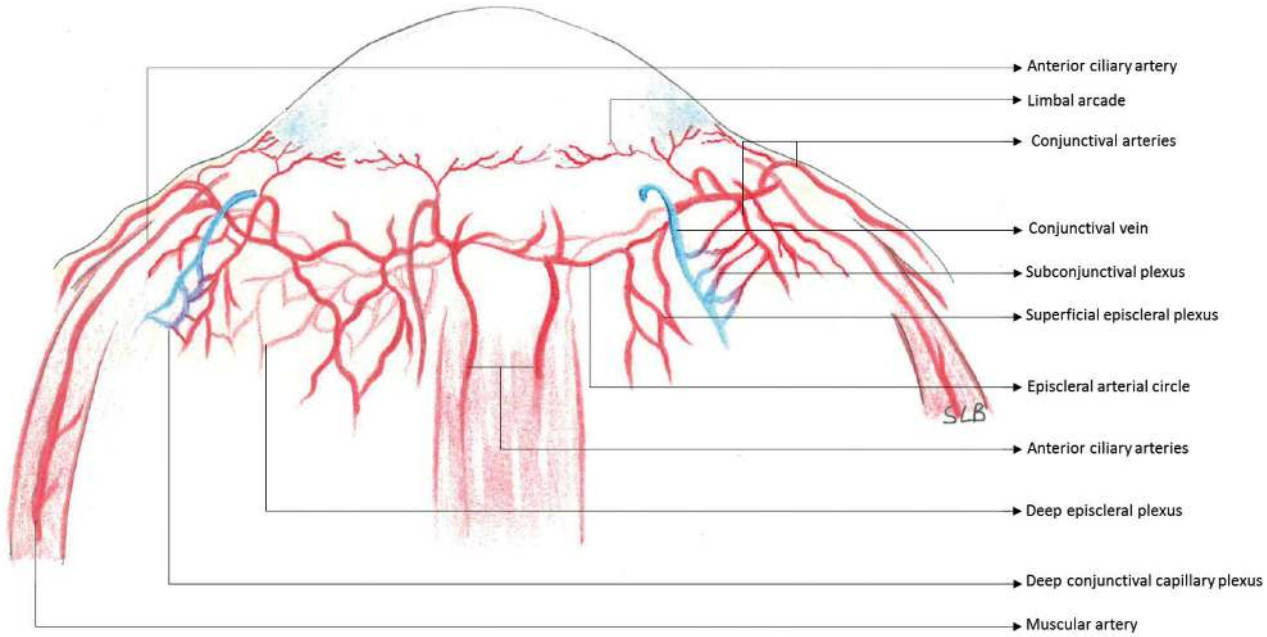


**Figure 96:** Blood supply to the limbus and cornea

According to McMonnies et al., 1982 the normal extent of limbal vessels measured from the limit of the visible iris was 0.13 mm inferiorly in non-lens wearers, 0.22 mm in RGP wearers and 0.47 mm in daily hydrogel lens wearers. In hydrogel extended wear, the vascular extent of limbal vessels into the cornea was 0.50–0.52 mm. Although the literature is ambivalent regarding the prevalence of CNV in contact lens wear, 10–30% of patients diagnosed with corneal neovascularisation wear contact lenses, while corneal neovascularisation develops in 1–20% of contact lens users. Patients who use rigid gas permeable (RGP) or PMMA lenses have a lower rate of neovascularisation and a higher prevalence has been reported in relation to soft contact lenses, especially in extended wear lenses [413].

**Terminology [120]**

A number of terms are used to describe the presence of blood vessels in the cornea:

- Vascularisation – normal capillaries extending no more than 0.2 mm into the clear cornea from the limbus
- Neovascularisation – formation and extension of vascular capillaries within and into previously clear cornea
- Limbal hyperaemia – distention of the limbal blood vessels either due to increased blood flow due to vessel dilation (active) or when drainage is hampered (passive), due to tight scleral lenses
- Vessel penetration – apparent ingrowth of blood vessels towards the corneal apex
- Vasoproliferation – increase in the number of blood vessels
- Vascular pannus – Connective tissue disposition and vascularisation between the epithelium and Bowman's membrane, usually in the superior limbal region
- Vascular response – any alteration to the normal vasculature, including the terms described above

**Classification**

The vascular plexus adjacent to the limbus is present at all levels of the cornea. Neovascularisation can best be described according to the level of the corneal tissue it affects; superficial, deep stromal and vascular pannus.

- Superficial neovascularisation (Figure 97)

  This is the most common vascular response induced by contact lenses. Normally episcleral branches of the anterior ciliary artery form a plexus around the limbus called the superficial marginal arcade. In contact lens wear, small branches form at right angles to this plexus, encroach the cornea looping inward toward the corneal apex. The vascular loops are semi-circular, they anastomose, each arc becoming smaller forming a rich vascular plexus around the limbus. New vessels often leak and a creamy lipid like fluid can be seen under high magnification around the vessels. Superficial neovascularisation can be extensive and interfere with vision if it encroaches the visual axis [414].

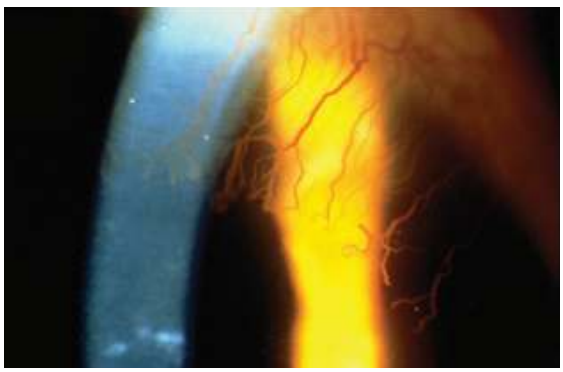

**Figure 97:** Superficial corneal neovascularisation

- Deep stromal neovascularisation (Figure 98)

  Contact lenses can induce CNV at any level of the cornea including the stroma, from just below Bowman's membrane to Descemet's membrane. It develops insidiously and progresses slowly without any symptoms. Stromal neovascularisation typically consists of a large feeding vessel that emerges from the limbus and enters the stroma. It develops into finer, tortuous branches that end in buds with numerous small vessel anastomoses. The vessels are generally derived from anterior ciliary arteries. Deep vessels may be arranged as terminal loops, brush, parasol, umbel, network or interstitial arcades (Figure 101). If the CNV is extensive enough and lipid leaks into the stroma, vision can be affected. Deep stroma CNV is often associated with other corneal pathology such as Herpes simplex or zoster keratitis, interstitial keratitis, disciform keratitis, deep corneal ulcer, chemical burns and sclerosing keratitis and grafts [413–416].

**Figure 98:** Deep stromal neovascularisation

- Vascular pannus (Figures 99–100)

  Pannus is an extensive ingrowth of tissue from the limbus onto the peripheral cornea. Pannus is Latin for "cloth" and the ingrowth of tissue frequently has the appearance of a cloth draped over the cornea. The penetration occurs between the epithelium and Bowman's membrane, separating these layers. This leads to destruction of Bowman's membrane. Micro-pannus is used if the invasion is less than 2 mm from the limbus [11]. Two forms exist; active or inflammatory pannus, which is avascular and composed of sub-epithelial inflammatory cells; and fibrovascular or degenerative pannus, which consist of an ingrowth of collagen and blood vessels often containing fatty plaques [353]. The invading end of the pannus often contains fibrotic tissue, it therefore stains brightly with Rose Bengal or Lissamine green.

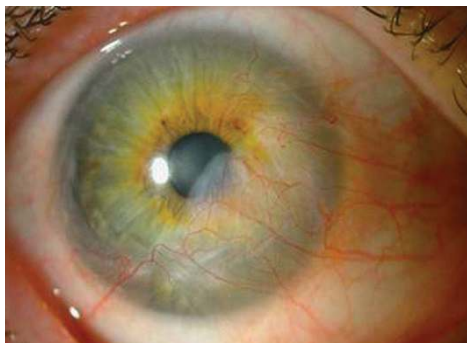

**Figure 99:** Severe vascular pannus

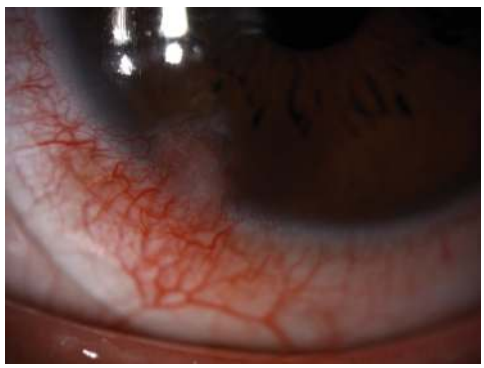

**Figure 100:** Corneal vascular pannus in a soft lens wearer

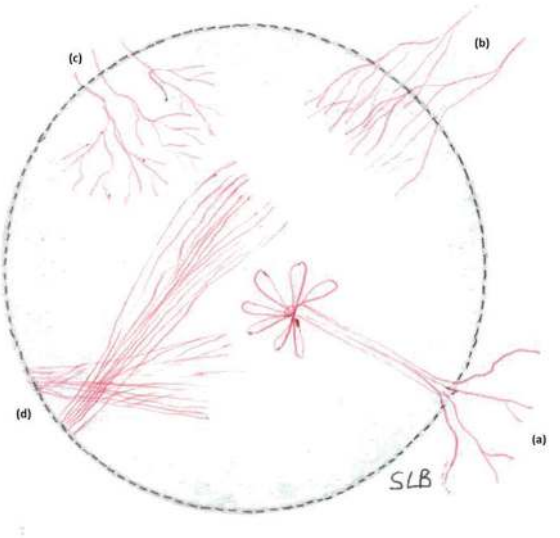


**Figure 101:** Corneal neovascularisation: (b) superficial, (c) terminal loop type, (d) brush type, (a) umbel type

**Risk Factors for CNV in Contact Lens Wear**

Intrinsic lens parameters including material properties (such as oxygen transmissibility) have an impact on the development of corneal neovascularisation. High myopia and astigmatism can probably influence the peripheral thickness of hydrogel lenses, which decreases peripheral oxygen transmissibility and enhances peripheral mechanical friction. This is also the case with prism ballasted soft lenses. Improper lens-corneal alignment, due to an exceedingly flat or steep cornea can result in peripheral hypoxic or mechanical trauma in soft lens wearers. Other causes for corneal neovascularisation include herpes simplex, stromal keratitis and corneal transplantation. Indeed, contact lenses are frequently used to address the refractive errors induced by herpetic corneal scars and are themselves associated with increased prevalence of herpetic attacks. Therefore, contact lens practitioners should be aware of recurrent corneal herpetic ulcers and address them promptly. The risk for corneal neovascularisation in post-penetrating keratoplasty patients, without active inflammation, increases in the presence of suture knots in the host stroma, active blepharitis or a large recipient bed. Therefore, the possible role of the contact lens, especially poor fitting lenses, in the development of corneal neovascularisation should be considered in these patients [21, 38, 367].

**Aetiology**

There is no single theory that can account for CNV. Rather, several factors may contribute. Proposed theories take the following aspects into account; metabolic factors (hypoxia, lactic acid, oedema, stromal softening), angiogenic suppression (necessity of substances that inactivate the normally present angiogenic inhibitors), vasostimulation (locally generated or introduced vasostimulatory factors such as free cellular elements, humoral components, epithelial cell factors, or extrinsic factors) and neural control (mediation of the vascular response to contact lens wear by contact lens-induced changes to corneal neurology). Another way of categorising stimuli that can promote vessel penetration into the normally avascular cornea includes nutritional, inflammatory, mechanical, traumatic and toxic factors. One or all of these stimuli are present during contact lens wear, particularly overnight wear [412, 417, 418]. Soft contact lens-induced hypoxia has been shown to stimulate the metabolism of arachidonic acid by a nicotinamide adenine dinucleotide phosphate (NADPH), cytochrome P-450 monooxygenase and 12 hydroxyeicosatrienoic acid (12-HETrE), which are pro-inflammatory and angiogenic factors. Biologic actions of this factor result in an increase in barrier permeability, vasodilatation, polymorphonuclear chemotaxis and vascular endothelial cell mitogenesis.

Routine contact lens wear is associated with inflammatory reactions and even in asymptomatic patients, can induce release of some pro-inflammatory cytokines, including interleukins 6 and 8. Hypoxia creates an environment in which epithelial cyclooxygenase activity is severely suppressed, whereas metabolising activity of cytochrome P-450-arachidonic acid or 12-lipoxygenase is maintained or enhanced. The 12 hydroxyeicosatetraenoic (12-HETE) produced by the corneal epithelium acts intracellularly to promote corneal oedema, whereas 12-HETrE acts in a paracrine manner to initiate an inflammatory cascade that can elicit neutrophil chemotaxis and neovascularisation of the cornea. Leukocyte migration into the stroma and release of angiogenic factors from these cells may subsequently promote new corneal vessel growth [417].

In summary: The contact lens creates tissue hypoxia, which leads to corneal oedema and stromal softening. The lens also contributes to mechanical trauma to the epithelium, this results in inflammation and the release of cytokines and prostaglandins, which are angiogenic. Inflammatory cells migrate to the area and release vasostimulating agents that initiate new vessel growth. The cellular distress signal, acts directly as a triggering agent with the vascular endothelial mesenchyme forming; endothelials, pericytes, fibroblasts and the smooth muscle of new blood vessels [11, 21, 367].

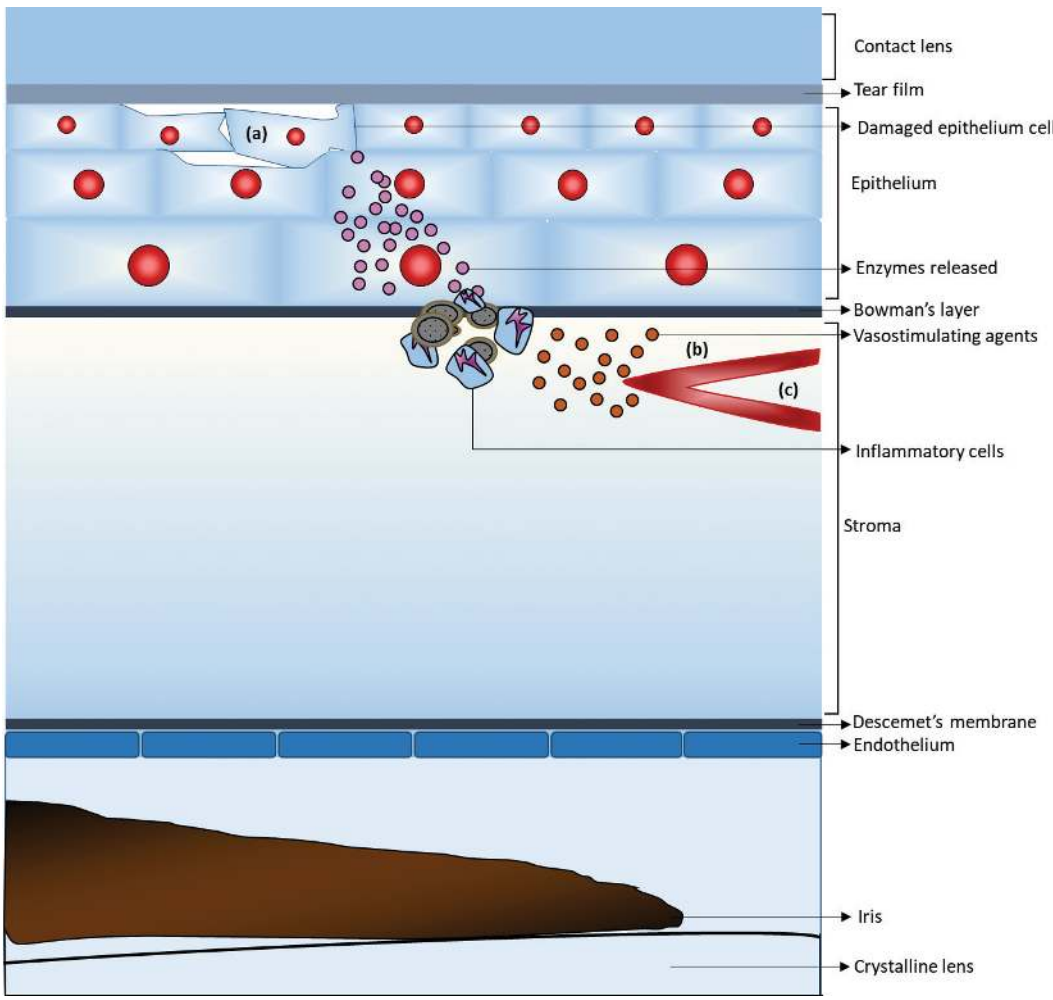


**Figure 102:** Hypothesised mechanism of corneal neovascularisation

(a) epithelial injury, (b) vasostimulating agents, (c) vessel growth. The contact lens creates tissue hypoxia which leads to corneal oedema and stromal softening. The lens also contributes to mechanical trauma to the epithelium which results in inflammation and the release of cytokines and prostaglandins which are angiogenic. Inflammatory cells migrate to the area and release vasostimulating agents that initiate new vessel growth. The cellular distress signal acts directly as triggering agent with the vascular endothelial mesenchyme forming; endothelials, pericytes, fibroblasts and the smooth muscle of new blood vessels

**Table 48:** Angiogenic molecules involved in corneal neovascularisation [412]

| Pro- and anti-angiogenic molecules in corneal neovascularisation. | |
|---|---|
| **Pro-angiogenic molecules** | **Anti-angiogenic molecules** |
| VEGF, PIGF<br>FGF<br>Angiopoietin<br>MMPs<br>PDGF<br>HIF<br>IGF<br>TGF-α, TGF-β<br>TNF-α<br>CTGF<br>IL-1, IL-8<br>MCP-1<br>Leptin<br>Integrins (αV β3)<br>Angiogenin<br>TXA, COX-2, NO<br>PAF<br>MMIF<br>HGF/SF<br>Heparanase | sVEGFR1<br>Endostatin<br>TSP-1, TSP-2<br>MMPs<br>TIMPs<br>PEDF<br>Angiostatin<br>IFN-γ<br>TNF-α<br>FasL<br>IL-4, IL-12, IL-13, IL-18<br>Tumistatin<br>Canstatin<br>Arrestin<br>PRL |
| MCP: Monocyte chemotactic protein; MMIF: Macrophage migratory inhibitory factor; MMP: Matrix metalloproteinase; NO: Nitrous oxide; PAF: Platelet activating factor; PIGF: Phosphatidylinositol-glycan biosynthesis class F protein; PRL: Prolactin; SF: Scatter factor; sVEGFR1: Soluble VEGF receptor-1; TIMP: Tumour inhibitor of metalloproteinase; TSP: Total serum protein; TXA: Thromboxane $A_2$. | |

### Management

Exchanging the lens with a more oxygen-permeable contact lens, changing wearing schedule from extended wear to daily wear, switching to RGP lenses instead of soft lenses and discontinuing contact lenses in cases of active progressive corneal new vessels are recommended. Anti-angiogenic therapy of the cornea (subconjunctival or intrastromal), as well as corticosteroids and non-steroidal anti-inflammatory agents, can help in cases with active neovascularisation that may endanger the survival of corneal graft or ocular surface health. Laser photocoagulation of new vessels, photodynamic therapy, electrocoagulation and stem cell transplant are surgical interventions recommended in severe cases [21, 367].

## INFILTRATIVE AND MICROBIAL KERATITIS

Very few of the complications of contact lens wear discussed in this chapter lead to a permanent loss of vision. Many conditions resolve with cessation of lens wear and corneal infiltrates without significant epithelial compromise or associated pathology and are usually benign. However, infiltrates are also a sign of microbial keratitis, which can cause permanent loss of vision if not managed timeously and appropriately. Microbial keratitis is a true ocular emergency.

### Definitions [120]

- Infiltrate - Material that has passed into tissue spaces or cells. It may include fluids, cells or other substances. 'Other substances may be natural (but occur in excess) or foreign to the tissue spaces or cells
- Infiltrative Keratitis - Inflammation of corneal tissue characterised by the presence of infiltrates
- Ulcerative Keratitis - Inflammation of corneal tissue characterised by extensive epithelial compromise, underlying epithelial and/or stromal infiltrates and possible stromal melting

- Microbial Keratitis - Inflammation of corneal tissue caused by direct involvement of microbial agents such as a bacteria, virus, fungus or protozoa
- Infectious Keratitis - Inflammation of cornea tissue attributable to the process of direct microbial infection
- Sterile Keratitis - Inflammation of cornea tissue attributable to processes other than direct microbial infection
- Culture positive – microorganisms positively identified from a culture or scraping of the affected tissue
- Culture negative – non-microorganisms identified from a culture or scraping of the affected tissue
- Intra-epithelial infiltrates – infiltrates (inflammatory cells) within the epithelium
- Sub-epithelial infiltrates – infiltrates (inflammatory cells) between Bowman's membrane and the epithelial basement membrane
- Stromal infiltrates – infiltrates (inflammatory cells) within the stroma

In most cases, infiltrates are sub-epithelial occurring in the anterior half of the stroma, or intra-epithelial. Areas of infiltrates appear as grey, grainy hazy areas with diffuse illumination and individual infiltrates can be visualised using indirect illumination [120]. The depth of the infiltrate can be determined using an optic section. The areas of infiltrates are often associated with localised areas of limbal or conjunctival redness. Essentially infiltrative keratitis caused by contact lenses can be divided into two forms; Sterile Infiltrative Keratitis and Microbial Keratitis (MK) [419]. MKs two most common causes are bacterial - *Pseudomonas aeruginosa* and protozoal – *Acanthamoeba.* Sterile Infiltrative Keratitis can be divided into five forms; Symptomatic Sterile Keratitis – Contact Lens Induced Peripheral Ulcer, Contact lens Induced Red Eye, Infiltrative Keratitis, Asymptomatic Sterile Keratitis – Asymptomatic Infiltrative Keratitis and Asymptomatic Infiltrates [419].

Infiltrates compromise mainly inflammatory cells, bacterial toxins, serum proteins and lipid leaking from the limbal vessels.

#### Sterile Infiltrative Keratitis

In sterile keratitis, there is no direct bacterial infection, in other words the bacteria do not gain entry and replicate within the cornea. The bacteria indirectly exert a pathogenic effect on the corneal tissue through enzyme or toxin (exotoxins and endotoxins) production, which activates the immune system, causing an inflammatory tissue response. Endotoxins consist of lipopolysaccharides and is a component of the outer membrane of the bacteria. Its presence causes antibody and cytokine production, neutrophil migration and complement activation. Exotoxins are excreted by microorganisms and cause inflammatory cells, such as PMNs to migrate from the limbal vessels to the affected tissue causing the typical signs of an infiltrative event [420].

#### Symptomatic Sterile Keratitis

##### *Contact Lens Induced Peripheral Ulcer (CLPU)*

CLPU is a unilateral inflammatory reaction of the cornea characterised by a focal excavation of epithelium, infiltrates and necrosis of anterior stroma. It is only seen in patients who wear lenses on an extended wear basis, often immediately upon awakening in the morning. A small, round peripheral infiltrate (0.5–1.0 mm in diameter), with slight surrounding infiltration is present in the mid-periphery of the cornea (Figure 103). The region of infiltration may extend from the limbal vessels beyond the location of the infiltrate, often in a triangular pattern. The infiltration is usually limited to the anterior stroma, but there may be some anterior chamber involvement [421–423]. In most cases, an erosion with full loss of the epithelium occur and the area stains brightly with NAFL with some diffusion of the dye into the surrounding tissue. Bowman's membrane usually remains intact. Symptoms include limbal and bulbar redness, tearing, photophobia, moderate-to-severe pain and foreign body sensation. Some may even report

seeing a white spot on their cornea. CLPU is a non-infectious, self-limiting event, probably caused by toxins secreted by gram-positive bacterial colonies on soft contact lenses. All the cases of CLPU are related to extended wear, and therefore the closed eye environment is also of aetiological significance [421, 423, 424].

CLPU should be managed by discontinuing contact lens wear, prescribing antibiotics and once resolved refitting the patient with high Dk/t lenses with an appropriate lens care system such as hydrogen peroxide. Consider daily disposable lenses. The prognosis of CLPU is good with most episodes resolving within 7 days, most within 2–3 days with appropriate treatment, but it will leave a dense circumscribed scar corresponding to the area of focal infiltrates. The scar has a typical "Bull's eye" appearance [21, 38].

**Table 49:** Signs of CLPU [38]

| Clinical signs of CLPU | |
|---|---|
| **Feature** | **Signs** |
| Corneal infiltrate<br>♦ Location<br>♦ Type<br>♦ Depth | Peripheral to mid-peripheral<br>Usually small, single, circular, dense yellowish-white focal infiltrate up to 2 mm<br>Anterior stroma, sub-epithelial |
| Surrounding cornea | Slight fine diffuse infiltration |
| Overlying epithelium | Commonly full thickness loss |
| Endothelium | Rarely involved |
| Anterior chamber reaction | Only if severe |
| Lid oedema | Uncommon |
| Bulbar/limbal redness | Moderate, severe in the region corresponding to the focal infiltrate |
| Unilateral/bilateral | Typically unilateral |

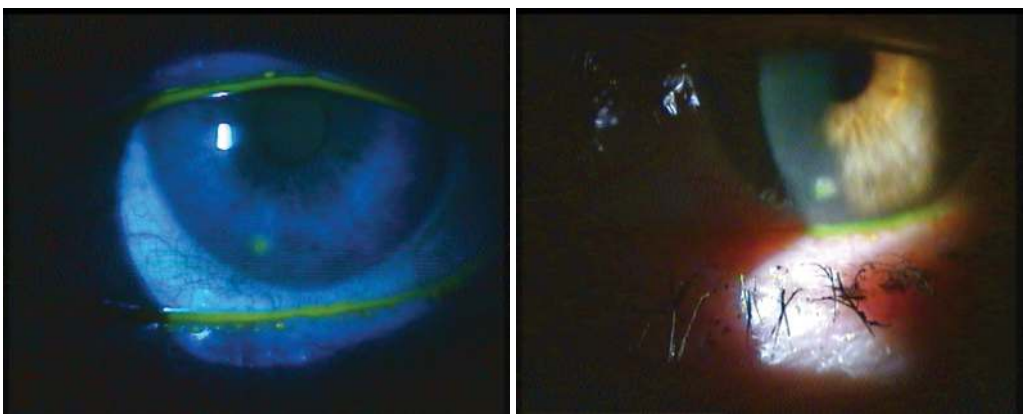

**Figure 103:** CLPU, left slide shows staining with NAFL and right is the same eye with normal white light

### *Contact Lens Acute Red Eye (CLARE)*

CLARE is an inflammatory reaction of the cornea and conjunctiva seen immediately after a period of extended wear of tightly adhering hydrogel lenses. A combination of multiple focal infiltrates and diffuse infiltration can be seen in the mid-periphery and periphery of the cornea, generally without any NAFL staining. The diffuse infiltration stems from the limbal vessels with no clear space between the infiltrates and the limbus, and the infiltrates are restricted to the epithelium and anterior stroma. Anterior chamber reactions are rare, and symptoms include moderate-to-severe

circum-limbal redness, irritation, moderate pain, photophobia and tearing. Patients are typically awakened by their symptoms or they are noticed after awakening. Vision can be affected in the acute phase but recovers quickly. CLARE is often bilateral. Both CLARE and CLPU are related to the hypoxic closed eye environment. Gram-negative bacteria, including *Pseudomonas aeruginosa*, accumulate in the biofilms on contact lenses. Toxins produced by these bacteria combined with the pro-inflammatory state of the closed eye environment are thought to contribute to the causes of CLARE [421, 425, 426].

CLARE should be managed by discontinuing contact lens wear, prescribing antibiotics, and once resolved refitting the patient with higher Dk/t lenses with an appropriate lens care system (hydrogen peroxide). Consider daily disposable lenses. The prognosis of CLARE is good with most episodes resolving within 3 days, most infiltrates clear within 7–14 days with appropriate treatment. Complete resolution can take up to 6 weeks. It rarely results in scar formation, but CLARE may recur with extended wear [21, 38].

**Table 50:** Clinical signs of CLARE [38]

| Clinical signs of CLARE | |
|---|---|
| **Feature** | **Signs** |
| Corneal infiltrate<br>♦ Location<br>♦ Type<br>♦ Depth | Peripheral to mid-peripheral<br>Fine, faint, cellular diffuse infiltration, sectorial or circumferential. Clusters of focal infiltrates interspersed amongst diffuse infiltration.<br>Anterior stroma, sub-epithelial |
| Surrounding cornea | Slight fine diffuse infiltration |
| Overlying epithelium | No significant staining, if present limited to punctate corneal staining |
| Endothelium | Uncommon |
| Anterior chamber reaction | Uncommon |
| Lid oedema | Uncommon |
| Bulbar/limbal redness | Moderate, to severe circumferential |
| Unilateral/bilateral | Typically, unilateral |

### *Infiltrative Keratitis (IK)*

IK is a unilateral inflammatory reaction of the cornea characterised by anterior stromal infiltration in the mid-periphery of the cornea, with or without epithelial involvement. Epithelial staining is usually punctate, but it may be severe enough to appear like a corneal erosion. IK is associated with both extended and daily wear lenses, but not extended wear (sleeping with lenses) and its symptoms are therefore rarely reported in the morning. Infiltrates are small and multiple and can be accompanied with mild-to-moderate diffuse infiltration. The infiltrates are typically sub-epithelial and there is no anterior chamber involvement. Symptoms include limbal redness, mild-to-moderate irritation, but rarely pain. A watery or purulent discharge may be present. The cause of IK differs from CLPU and CLARE, as it is not associated with the closed eye environment. However, toxins released from bacteria adherent to the lens biofilms plays a role in the aetiology [421, 427, 428].

IK should be managed by discontinuing contact lens wear, prescribing antibiotics, and once resolved refitting the patient with high Dk/t lenses with an appropriate lens care system such as hydrogen peroxide. Consider daily disposable lenses. The prognosis of IK is good with most episodes resolving within 14 days, the greater the severity of the infiltrates the longer the recovery. IK rarely results in scar formation [21, 38].

**Table 51:** Clinical signs of IK [38]

| Clinical signs of IK | |
|---|---|
| **Feature** | **Signs** |
| Corneal infiltrate<br>♦ Location<br>♦ Type<br>♦ Depth | Peripheral to mid-peripheral<br>Corneal erosion or defect with underlying diffuse infiltration, possibly small infiltrates<br>Anterior stroma, sub-epithelial |
| Surrounding cornea | Slight fine diffuse infiltration |
| Overlying epithelium | Slight to severe staining |
| Endothelium | Uncommon |
| Anterior chamber reaction | Uncommon |
| Lid oedema | Uncommon |
| Bulbar/limbal redness | Slight to moderate and localised. |
| Unilateral/bilateral | Typically, unilateral |

## Asymptomatic Sterile Keratitis

### *Asymptomatic Infiltrative Keratitis (AIK)*

AIK is an inflammatory event, characterised by infiltration of the cornea without pain. Although the condition is typically unilateral it can affect both eyes at the same time. It is seen with daily and extended wear lenses. Signs include small focal, often multiple infiltrates in the peripheral cornea up to 0.40 mm in diameter, with or without diffuse infiltration. Punctate staining is often present and there may be mild-to-moderate limbal redness. However, there will be no anterior chamber reaction. Patients are often completely unaware of the condition. It is thought that AIK is the result of the corneas normal protective cellular response to contact lens wear, while others have postulated that it is caused by toxins from gram-negative bacteria [429–432].

AIK should be managed by discontinuing contact lens wear, prescribing antibiotics if needed, and once resolved refitting the patient with high Dk/t lenses with an appropriate lens care system such as hydrogen peroxide. Consider daily disposable lenses. The prognosis of AIK is good [21, 38].

**Table 52:** Clinical signs of AIK [38]

| Clinical signs of AIK | |
|---|---|
| **Feature** | **Signs** |
| Corneal infiltrate<br>♦ Location<br>♦ Type<br>♦ Depth | Peripheral to mid-peripheral<br>Mild to moderate fine diffuse infiltration, possibly small focal infiltrates<br>Anterior stroma, sub-epithelial |
| Surrounding cornea | Slight fine diffuse infiltration |
| Overlying epithelium | Punctate staining |
| Endothelium | Uncommon |
| Anterior chamber reaction | Uncommon |
| Lid oedema | Uncommon |
| Bulbar/limbal redness | Slight to moderate and localised |
| Unilateral/bilateral | Typically, unilateral |

### *Asymptomatic Infiltrates (AI)*

AIs are infiltrates that appear in the cornea with no apparent signs or symptoms. They can be unilateral or bilateral, with daily or extended wear lenses. The infiltrates are typically small and focal (<0.20 mm in diameter), mild infiltration may be present, but there is no epithelial staining. There is no anterior chamber involvement and some authors believe that AI does not represent a true inflammatory event. AI may be a normal occurrence coincidental with lens wear [429–432].

AI should be managed by discontinuing contact lens wear, prescribing antibiotics if needed, and once resolved refitting the patient with high Dk/t lenses with an appropriate lens care system such as hydrogen peroxide. Consider daily disposable lenses. The prognosis of AI is good [21, 38].

**Table 53:** Clinical signs of AI [38]

| Clinical signs of AI | |
|---|---|
| **Feature** | **Signs** |
| Corneal infiltrate<br>♦ Location<br>♦ Type<br>♦ Depth | Peripheral, can be present anywhere on the cornea<br>Small focal infiltrates (0.2 mm in size), mild or diffuse infiltration<br>Anterior stroma, sub-epithelial |
| Surrounding cornea | Slight fine diffuse infiltration |
| Overlying epithelium | Epithelium is intact |
| Endothelium | Uncommon |
| Anterior chamber reaction | Uncommon |
| Lid oedema | Uncommon |
| Bulbar/limbal redness | Uncommon |
| Unilateral/bilateral | Typically, unilateral but can be bilateral |

## MICROBIAL KERATITIS (MK)

Microbial keratitis is the most severe reaction that can occur in response to contact lens wear. It is progressive and potentially devastating to the cornea often resulting in vision loss. Microbial keratitis is defined as an inflammation of corneal tissue through direct infection by a microbial agent, such as a bacteria, virus, protozoa or fungus. The term infectious keratitis and corneal ulcer is synonymous with MK [120].

Although the cornea has natural defence mechanisms (discussed in chapter 2) that protects it from microbial infection, contact lens wear increases the risk of infection. The incidence of MK in contact lens wear is difficult to determine and is derived from clinical surveys, pre-market clinical trial data and retrospective studies. What is clear is that the incidence of MK is greater with extended wear of both disposable and conventional hydrogel lenses in comparison to silicone hydrogel and RGP lenses [21, 38, 367, 433]. Estimates for the incidence of MK for daily wear of RGP lenses ranges from 0.4–4 per 10000 patients per year and 0.2 per 10000 with extended wear of RGP lenses [38, 434]. Holden et al., 2003 estimated the incidence of MK in patients wearing silicone hydrogel lenses on an extended wear basis at 0.53 per 10000 [435]. Guillion et al., 1994 found a much higher incidence of MK per 10000 daily soft lens wearers in the UK, 39 for daily conventional soft lens wearers and 18 for disposable lens wearers [436]. Using this data from Guillion et al. as well as that of other authors one can estimate that **the average contact lens practitioner who sees 10 conventional soft lens patients per week will see at least 2 cases of MK per year [21, 38, 436].**

The relative risk of developing MK with contact lens wear according to Matthews et al., 1992 is [437]:

- Daily wear conventional hydrogel lenses – 1:1
- Extended wear conventional hydrogel lenses – 2:6
- Daily wear disposable hydrogel lenses – 4:1
- Extended wear disposable hydrogel lenses – 8:1

These findings were corroborated by Buehler et al., 1992 who reported the risk of developing MK as [438]:

- Daily wear conventional soft lenses – 1:0
- Extended wear Conventional soft lenses – 2:8
- Extended wear disposable soft lenses – 3:9

Both confirm the greater risk of MK with extended wear lenses of any modality.

### Why is Contact Lens Wear Associated with an Increased Risk of MK?

The simple answer is the presence of microorganisms in the biofilms that exists on the lenses, as well as the mechanical and hypoxic trauma caused by the lenses, which compromise the corneal defences against infection [45, 46]. Other factors that play a role are inefficiency of contact lens solutions, patient non-compliance, poor lens case care, poor patient hygiene and swimming with lenses [21, 367, 437, 439]. The initial step in the pathogenesis of MK with hydrogel extended wear lenses involves the colonisation of the contact lens with microbes and the formation of a biofilm [45]. Studies have shown that organisms, such as *Pseudomonas* and *Acanthamoeba* adhere to hydrogel lenses. Beattie et al., 2006 found that *Acanthamoeba* readily attaches to silicone hydrogel lenses. These organisms can under suitable conditions adhere to, damage or invade the epithelium and replicate in the corneal stroma. This leads to a cascade of inflammatory events culminating in tissue inflammation, destruction and a dense corneal infiltrate [440].

**Table 54:** Clinical signs of MK [38]

| Clinical signs of MK | |
|---|---|
| **Feature** | **Signs** |
| Corneal infiltrate<br>♦ Location<br>♦ Type<br>♦ Depth | Mainly central or paracentral, sometimes peripheral<br>Large, dense, irregular infiltrate > 1 mm<br>Multiple or focal<br>Anterior to mid stroma, may involve entire depth of cornea, ulceration and necrosis in severe disease |
| Surrounding cornea | Involved, ranges from oedema, diffuse infiltrates to satellite lesions and ring infiltrates |
| Overlying epithelium | Commonly full thickness loss |
| Endothelium | Ranges from none to dusting with cells and keratic precipitates |
| Anterior chamber reaction | Common, ranging from flare to hypopion |
| Lid oedema | Usual, blepharospasm may be present |
| Bulbar/limbal redness | Severe, conjunctival chemosis may be present |
| Unilateral/bilateral | Typically, unilateral |

The simple flow chart (Figure 104) illustrates the sequence of events leading to MK.

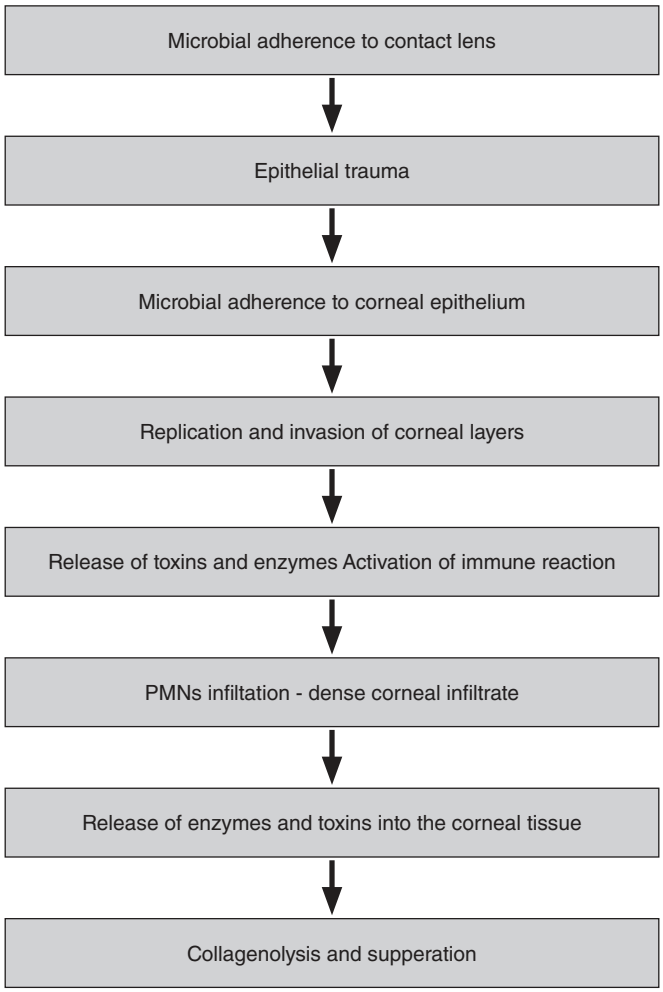


**Figure 104:** Sequence of events leading to MK [38]

The normal flora of the conjunctiva and anterior eye includes the following bacteria [100, 441]:
Gram-positive

- *Staphylococcus aureus*
- *Staphylococcus epidermidis* which is the most common bacteria found
- *Streptococcus pneumoniae* which is found occasionally
- *Corynebacterium diphtheria* which is more common in > 20–year-old individuals
- *Propionibacterium acnes* which is an anaerobe from the skin

Gram-negative

- *Haemophilus influenza*
- *Escherichia coli*
- *Pseudomonas aeruginosa*

Contact lens wear and contact lens solutions can alter this flora, which may also contribute to the increased risk of MK in contact lens wear. The bacterial diversity of the conjunctiva is higher than that of the skin. Moreover, the conjunctiva had a microbial diversity similar to the oral microbiota. These results are remarkable, considering the antimicrobial effects of tear compounds [442]. Shin et al., 2016 showed that the eye microbiota of lens wearers is

different from that of non-wearers, resembling more closely the microbiota of the skin under the eye, which is lower than that of the non-lens wearing eye [442].

Table 53 lists the most common microorganisms causing infectious eye disease. *Staphylococcus spp*. commonly cause bacterial conjunctivitis and infiltrative keratitis including MK, but the most devastating MK is caused by *Pseudomonas* and *Acanthamoeba* infection. Generally, corneal ulcers associated with gram-positive bacteria are usually smaller and less purulent compared to those associated with gram negative bacteria.

**Table 55:** Common pathogens causing infectious disease of the eye [100]

| Gram positive bacteria | Gram negative bacteria | Viral | Chlamydial | Fungal | Amoebic |
|---|---|---|---|---|---|
| **Staphylococcus aureus** | Heamophillus influenzae | Adenoviruses | Chlamydia trachomatis | Candida albicans | Acanthamoeba castellani |
| **Staphylococcus epidermidis** | Neisseria gonorrhoeae | Herpes zoster | | Aspergillus species | |
| **Streptococcus pneumonia** | Pseudomonas aeruginosa | Enterovirus 70 | | | |
| **Streptococcus pyogenes** | Proteus mirabilis | Esptein -Barr | | | |
| **Corynobacterium diphteria** | Moraxella catarrhalis | Herpes simplex | | | |
| | Moraxella lacunata | | | | |

### More About these Disease Causing Microorganisms [443]

#### Gram-Positive Bacteria

#### *Staphylococcus Epidermidis*

*Staphylococcus epidermidis* is a gram-positive bacterium, and one of over 40 species belonging to the genus Staphylococcus. It is a part of the normal human flora, typically the skin flora and less commonly the mucosal flora. Although *Staph. epidermidis* is not usually pathogenic, patients with compromised immune systems are at risk of developing infection. *S. epidermidis* is a very hardy microorganism, consisting of non-motile, gram-positive cocci, and is arranged in grape-like clusters. It forms white, raised and cohesive colonies about 1–2 mm in diameter after overnight incubation and is not haemolytic on blood agar. It is a catalase-positive, coagulase-negative, facultative anaerobe that can grow by aerobic respiration or by fermentation [444, 445].

The ability to form biofilms on plastic devices is a major virulence factor for *Staph. epidermidis*. One probable cause is surface proteins that bind blood and extracellular matrix proteins. It allows other bacteria to bind to the already existing biofilm, creating a multilayer biofilm. Such biofilms, decrease the metabolic activity of bacteria within them [446]. This decreased metabolism, in combination with impaired diffusion of antibiotics, makes it difficult for antibiotics to effectively clear this type of infection.

#### *Staphylococcus Aureus*

*Staphylococcus aureus* is an aerobic, gram-positive, round-shaped bacterium and it is a member of the normal flora of the body, frequently found in the nose, respiratory tract and on the skin. It is often positive for catalase and nitrate reduction and is a facultative anaerobe that can grow without the need for oxygen. Although *S. aureus* is not always pathogenic (and can commonly be found existing as a commensal), it is a common cause of skin infections including abscesses, respiratory infections such as sinusitis and food poisoning [447]. Pathogenic strains

often promote infections by producing virulence factors, such as potent protein toxins and the expression of a cell-surface protein that binds and inactivates antibodies [445, 447].

*Staph. aureus* is catalase-positive (meaning it can produce the enzyme catalase). Catalase converts hydrogen peroxide ($H_2O_2$) to water and oxygen. *Staph. aureus* is often found in biofilms formed on medical devices implanted in the body or on human tissue. It is commonly found with another pathogen, *Candida albicans*, forming multispecies biofilms. The latter is suspected to help *Staph. aureus* penetrate human tissue [448].

Depending on the strain, *Staph. aureus* is capable of secreting several exotoxins. Many of these toxins are associated with specific diseases [449]. **It is the most common cause of bacterial conjunctivitis and blepharitis in the western world and is transmitted by direct hand to eye contact.** *Staph. aureus* is associated with marginal infiltrates and corneal phlyctenules [450]. The ulcers tend to be round or oval, well demarcated and remains localised with distinct borders. Furthermore, the ulcer tends to develop slowly more in depth than in width. It is associated with a moderate discharge and hypopyon [11].

***Streptococcus Pneumoniae***

*Streptococcus pneumoniae* or pneumococcus, is a gram-positive, alpha-haemolytic (under aerobic conditions) or beta-haemolytic (under anaerobic conditions), anaerobic bacteria. The bacteria are usually found in pairs (diplococci) and do not form spores and are non-motile. As a significant human pathogenic bacterium *Strep. Pneumoniae* was recognised as a major cause of pneumonia in the late 19$^{th}$ century and is the subject of many humoral immunity studies. *Strep. pneumoniae* resides asymptomatically in healthy carriers typically colonising the respiratory tract, sinuses and nasal cavity of 50% of the population. However, in susceptible individuals with weaker immune systems, such as the elderly, HIV positive and young children, the bacterium may become pathogenic and spread to other locations to cause disease. It spreads by direct person-to-person contact via respiratory droplets and by autoinoculation in persons carrying the bacteria in their upper respiratory tract [445].

The bacterium is surrounded by a polysaccharide capsule, which protects against phagocytosis. It tends to cause acute, purulent infections, due to endotoxin production [445]. Pneumococcal corneal ulcers frequently occur after trauma or dacryocystitis. The keratitis may be localised, or it can spread in one direction, usually centrally. The ulcer has indistinct "fuzzy" edges and is accompanied by marked anterior chamber reaction including hypopion. Corneal perforation is common [11].

***Streptococcus Pyogenes***

*Streptococcus pyogenes* is a species of gram-positive bacteria. These bacteria are aero-tolerant and extracellular, made up of non-motile and non-sporing cocci. As expected streptococci is clinically important in human illness. It is an infrequent, but usually pathogenic part of the skin microbiota.

Like other cocci, streptococci are round bacteria. The name is derived from Greek words meaning chain (Strepto) of berries (coccus) and pus (pyo) forming (genes), because streptococcal cells tend to link in chains of round cells. A number of infections caused by the bacterium, produce pus. Streptococci are catalase-negative. The bacteria are spread via respiratory droplets and hand contact with nasal discharge and skin contact with impetigo lesions [445].

*Strep. pyogenes* is the cause of many important human diseases, ranging from mild superficial skin infections to life-threatening systemic diseases. Infections typically begin in the throat or skin. The most striking sign is a strawberry-like rash. Examples of mild *Strep.pyogenes* infections, include pharyngitis (strep throat) and localised skin infection (impetigo). Erysipelas and cellulitis are characterised by multiplication and lateral spread of *Strep. pyogenes* in deep layers of the skin. *Strep. pyogenes* invasion and multiplication in the fascia can lead to necrotising fasciitis, a life-threatening condition requiring surgery. Infections, due to certain strains of *Strep. pyogenes* can be

associated with the release of bacterial toxins. Throat infections associated with release of certain toxins lead to scarlet fever. Other toxigenic *Strep. pyogenes* infections may lead to streptococcal toxic shock syndrome, which can be life-threatening [445].

*Strep. Pyogenes* is a common ocular infection associated with severe inflammation and membrane formation due to endotoxin production. It causes diffuse rapidly spreading cellulitis that extend along the lymphatic pathway into the bloodstream leading to septicaemia [11].

**Gram-Negative Bacteria**

***Pseudomonas Aeruginosa***

*Pseudomonas aeruginosa* is a common gram-negative, rod-shaped, bacterium that can cause diseases in plants and animals, including humans. A species of considerable medical importance, *P. aeruginosa* is a multidrug resistant pathogen recognised for its ubiquity, its intrinsically advanced antibiotic resistance mechanisms and its association with serious illnesses. The organism is considered opportunistic insofar as serious infection often occurs during existing diseases or conditions – most notably cystic fibrosis and traumatic burns. It is also found generally in the immunocompromised, but can infect the immunocompetent. Treatment of *P. aeruginosa* infections can be difficult, due to its natural resistance to antibiotics. When more advanced antibiotic drug regimens are needed, adverse effects may result [445, 451].

It is citrate, catalase and oxidase positive. It is found in soil, water, skin flora and most man-made environments throughout the world. It thrives not only in normal atmospheres, but also in low-oxygen atmospheres, thus has colonised many natural and artificial environments. It uses a wide range of organic material for food. In animals, its versatility enables the organism to infect damaged tissues or those with reduced immunity. The symptoms of such infections are generalised inflammation and sepsis. If such colonisations occur in critical body organs, such as the lungs, the urinary tract and kidneys, the results can be fatal. Because, it thrives on moist surfaces, this bacterium is also found on and in medical equipment, including catheters and contact lenses causing cross-infections in hospitals and clinics. *P. aeruginosa* is not extremely virulent in comparison with other major pathogenic bacterial species such as *Staphylococcus aureus* and *Streptococcus pyogenes, however*, *P. aeruginosa* is capable of extensive colonisation and can aggregate into enduring biofilms [445, 451].

Biofilms seem to protect these bacteria from adverse environmental factors. *P.aeruginosa* produces glycocalyx associated with bacterial adhesion, persistence, and survival in infected tissues and on surface of contact lenses. The glycocalyx also protects the pathogen from immune cells and antibiotics. *P. aeruginosa* can survive over wide temperature range, 10–42ºC and even grow in an anaerobic environment rich in nitrates. It is an opportunistic pathogen that causes a rapidly spreading, severely destructive corneal ulcer. However, surface damage of the epithelium must be present for *P. aeruginosa* adherence and infection [45]. Exotoxins and endotoxins are liberated and inhibit protein synthesis similar to the diphtheria toxin. Rapid death of epithelium, stroma and endothelium cells and necrosis results. The ulcer spreads rapidly and perforation of the cornea can occur within 2 to 5 days. The cornea has a diffuse ground glass appearance and a copious mucopurulent discharge with a greenish colour adheres to the surface of the ulcer. An anterior chamber reaction and hypopion is usually is present. Ring infiltrates are common and a necrotising enzyme, proteoglycanase, rapidly causes stromal destruction with descemetocele [11]. Two types of *P.aeruginosa* cause clinical disease and the pathogenesis of the two types are entirely different. One type (invasive strain) invades the corneal epithelial cells without killing them, therefore causing the disease largely through the host cell immune response. The other type is cytotoxic (cytotoxic strain) to the corneal and other epithelial cells, killing the hosts cells [45, 452].

***Serratia Marcecens***

*Serratia marcescens* is a species of rod-shaped, gram-negative bacteria in the family Enterobacteriaceae. It is commonly found in the respiratory and urinary tracts of hospitalised adults and in the gastrointestinal system of children. Due to its abundant presence in the environment, and its preference for damp conditions, *S. marcescens* is commonly found growing in bathrooms; especially on tile grout, shower corners, toilet water line and wash basin; where it manifests as a pink, pink-orange or orange discoloration and slimy film feeding off phosphorus-containing materials or fatty substances, such as soap and shampoo residue [445, 453].

Once established, complete eradication of the organism is often difficult, but can be accomplished by application of a bleach-based disinfectant. Rinsing and drying surfaces after use can also prevent the establishment of the bacterium by removing its food source and making the environment less hospitable. *S. marcescens* may also be found in environments, such as dirt, supposedly "sterile" places, and the subgingival biofilms found on teeth. Due to this, and because *S. marcescens* produces a reddish-orange tripyrrole pigment called prodigiosin, it may cause staining of the teeth [445, 453]. *S. marcescens* is a motile organism and can grow in temperatures ranging from 5–40 °C and in pH levels ranging from 5 to 9. It is differentiated from other gram-negative bacteria by its ability to perform casein hydrolysis, which allows it to produce extracellular metalloproteinases, which are believed to function in cell-to-extracellular matrix interactions [453]. In humans, *S. marcescens* can cause an opportunistic infection in several sites, including the unary tract, respiratory tract, wounds and the eye, where it may cause conjunctivitis, keratitis, endophthalmitis and tear duct infections. *S. marcescens* can cause liquefaction keratitis, necrosis and perforation of the cornea [11].

***Viruses***

All viral diseases are neurotrophic, afferent sensation is compromised for many months after treatment. Viral infections associated with contact lens wear are fortunately rare but do occur. They include the Herpes simplex virus causing dendritic ulcers and adenoviral infections causing epidemic keratoconjunctivitis and is typical sub-epithelial infiltrates [21].

***Fungi [454]***

A study by Gray et al., 1995 found that 24% of contact lens cases were colonised by fungi with a majority growing *Cladosporium* species or *Candida* species. Other fungi that were also isolated include *Fusarium solani, Aspergillus versicolor*, *Exophiala*, and *Phoma*. Most of the fungi contaminants were also found to be associated with bacterial contaminants [105]. Fungal keratitis is frequently seen in immune-compromised hosts (HIV, AIDS), with oral or topical steroid users and in patients on chemotherapy for cancer. Fungi are notorious as lacrimal apparatus infector and cause dirty greyish raised infiltrates in the peripheral cornea. The ulcers are typically serpiginous with feathered edges [11].

Factors which contribute to fungal contamination of contact lenses include, but are not limited to, hygiene and negligence, such as [105]:

- Improper sterilisation and disinfection of contact lenses
- Use of contaminated lenses
- Contaminated contact lens case
- Contaminated contact lens solution
- Wearing of "contact lenses during eye infections
- Introduction of microorganisms from the environment

Studies suggest a number of recommendations for contact lens wearers to prevent contamination by both bacterial and fungal contaminants, which include [105]:

- Cleaning the contact lens case by scrubbing the interior of the case to disrupt biofilms
- Rinsing the contact lens case with very hot water, temperatures greater than 70 °C, which will kill *Acanthamoeba* contaminants
- Allow contact lens cases to air dry between uses
- If using hydrogen peroxide as a disinfecting agent, use a two-step system
- And lastly, replace contact lens case regularly

**Protozoa**

**Acantamoeba Keratitis**

*Acanthamoeba* keratitis, first recognised in 1973, is a rare, vision threatening, parasitic infection seen most often in contact lens wearers. It is often characterised by pain out of proportion to findings and the late clinical appearance of a stromal ring-shaped infiltrate. It is both difficult to diagnose and difficult to treat. Two of the eight known species of *Acanthamoeba*, *A. castellanii* and *A. polyphaga*, are responsible for most infections. *Acanthamoeba* are commonly found as free-living amoeba that have been located in various environments including pools, hot tubs, tap water, shower water and contact lens solution [455]. Risk factors include contact lens wear, exposure to organism (often through contaminated water) and corneal trauma. It is thought that over 80% of *Acanthamoeba* keratitis appears in contact lens wearers. In one study, 75% of the patients were contact lens wearers; 40% wore daily soft lenses, 22% wore rigid gas permeable lenses and 38% wore extended wear or other lenses. *Acanthamoeba* is ubiquitous. Corneal trauma, followed by exposure to the parasite (often through a water supply or contact lens solution) in a patient with low tear levels of anti-*Acanthamoeba* IgA leads to infection [456]. *Acanthamoeba* exist in two forms; active trophozoites (25–40 μm); and dormant cysts (13–20 μm). The trophozoites are mobile and consume bacteria, yeasts, algae and small organic particles. The trophozoites form double walled cysts, which are incredibly resistant to methods of eradication (including freezing, heating, chlorination, and irradiation)[457]. The cysts can survive *in vitro* for more than 20 years [457]. When the environmental conditions are appropriate, the cysts turn into trophozoites, which produce a variety of enzymes that aid in tissue penetration and destruction [457]. Since treatment is toxic, lengthy, and not necessarily effective, prevention is essential. Both trophozoites and cysts can adhere to the surface of soft and rigid contact lenses. Any breaks in the corneal epithelium or loss of corneal defence mechanisms, may allow them to invade the corneal tissue [457]. Importantly, both trophozoites and cysts can harbour a variety of microorganisms including *Pseudomonas spp, salmonella, mycobacterium* and others, which may enhance the attachment of the trophozoite to hydrogel contact lenses and cause co-infections [457]. Contact lens wearers should be taught how to clean their contact lenses properly. They should be instructed never to use tap water or even saline to clean their lenses. They should also be instructed to visit an optometrist or ophthalmologist at the earliest sign of problems [455].

Early signs may be mild and non-specific, and the disease progresses slowly. Possible findings include epithelial irregularities, epithelial or sub-epithelial infiltrates and pseudodendrites. Later signs include stromal infiltrates (ring-shaped, disciform or numular), satellite lesions, epithelial defects, radial keratoneuritis, scleritis and anterior uveitis (with possible hypopyon). The radial keratoneuritis is due to the trophozoites clustering around corneal nerves and is pathogonomic for *Acanthamoeba* keratitis. Careful slit lamp examination is necessary to identify these infiltrative lesions, which occur in up to 63% of all cases of *Acanthamoeba* keratitis [457]. Advanced signs include stromal thinning and corneal perforation. *Acanthamoeba* keratitis is characterised

by pain out of proportion to the clinical signs. Patients often complain of pain, decreased vision, redness, foreign body sensation, photophobia, tearing and discharge. Symptoms may wax and wane and they may be quite severe at times [455, 457].

The differential diagnosis for *Acanthamoeba* in its early clinical stages includes dry eye, herpes simplex virus keratitis, recurrent corneal erosion, staph marginal keratitis and contact lens associated keratitis. The differential diagnosis of later clinical stages includes viral, bacterial, fungal and sterile (such as from topical anaesthetic abuse) keratitis [455].

Medical treatment for *Acanthamoeba* keratitis is still evolving and extremely challenging. Early diagnosis ensures a good prognosis and vision recovery [457]. Different regimens include topical preparations of Brolene (Propamidine isethionate 0.1%), Neomycin-Polymyxin B-Gramicidin, polyhexamethylene biguanide 0.02% (PHMB), chlorhexadine, voriconazole, cycloplegia, topical steroids and analgesics. Some practitioners recommend oral ketoconazole [373]. Medications have to be used for a long period after recovery to prevent relapses because the drugs are less effective against the cystic form [457].

## MEDICAL TREATMENT STRATEGY FOR INFILTRATIVE AND MICROBIAL KERATITIS [373]

According to the Wills Eye Manual (International 6th edition) all ulcers and infiltrates are treated as bacterial unless there is a high index of suspicion of another form of infection. When dealing with microbial keratitis, signs and symptoms are usually good indicators of the severity of the infection – the more severe the symptoms and the redder the eye, the more likely it is that the infection is serious and needs urgent medical intervention. Therefore, when dealing with infiltrates remember to look at ***"the company it keeps"*** when making your diagnosis and deciding on an appropriate management plan. Always remember that inflammation is worse in bacterial keratitis, due to the release of exotoxins with replication and endotoxins after cell death, which causes ring infiltrates. Enzymes, collagenases, coagulase, proteases, nucleases, lipases, elastase, fibrinolysins and hemolysins are also released.

The Wills Eye Manual suggest the following treatment protocol, when dealing with suspected bacterial keratitis:

- Cycloplegia to improve comfort and prevent synechiae
- If a hypopion is present, 1% atropine tid should be used
- Culture to identify the organism

Topical antibiotics should be administered according to the following algorithm:

### Small non-staining peripheral infiltrates with minimal anterior chamber involvement and discharge and low risk of vision loss

**Non-Contact Lens Wearer**

- Broad spectrum topical antibiotics, fluoroquinolones - moxifloxacin, gatifloxacin, besifloxacin, levofloxaxin or ciprofloxacin q1–2 h

**Contact Lens Wearer**

- Fluoroquinolone - moxifloxacin, gatifloxacin, besifloxacin, levofloxaxin or ciprofloxacin q1–2 h
- Add tobramycin or ciprofloxacin ointment qhs – note if using ointment more than qid use ciprofloxacin rather than tobramycin due to its potential corneal toxicity

**Medium size (1–1.5 mm), peripheral infiltrate with overlying epithelial defect, anterior chamber reaction and discharge and borderline risk of vision loss**

- Fluoroquinolone - moxifloxacin, gatifloxacin, besifloxacin, levofloxaxin or ciprofloxacin q1h q 1 h around the clock
- Consider starting with loading dose of q5 minutes for 5 doses, then q30 until midnight and then q1h
- Mofloxacin has better gram-positive coverage, gatifloxacin and ciprofloxacin is better against *Pseudomonas* and *Seratia*

**Vision threatening – any ulcer larger than 1–2 mm in the visual axis which is unresponsive to treatment**

- Fortified tobramycin or gentamycin (15 mg/ml), cefalozin (50 mg/ml) and vancomycin (25 mg/ml) every 30 to 60 minutes alternating with fortified cefazolin or vancomycin q1h
- Vancomycin should be reserved for resistant organisms
- All vision threatening ulcers are treated with loading doses q5 minutes for 5 minutes and the q30–60 minutes around the clock
- Consider a protective shield – not a patch
- No contact lens wear and add pain medication as needed
- Oral fluoroquinolones (ciprofloxacin 500 mg p.o bid and mofloxacin 400 mg p.o qid) penetrate the cornea well and may have added benefits for patients with scleral involvement or impending perforation
- Admission to hospital if:

Infection is sight threatening, patient is non-compliant, suspected topical anaesthetic abuse, intravenous antibiotics are needed

- Follow-up

Daily until pain resolves, epithelial defect reduces, and anterior chamber reaction subsides.

- Check IOP
- Taper treatment once improvement is noticed, never dose antibiotics less than qid to avoid resistance

Topical steroids are used in some case only after the organism is identified, infection is under control and severe inflammation persists

**"WHEN IN DOUBT, SEND IT OUT"**

## ANTIBIOTICS

The only absolute indication for a topical antibiotic is microbial keratitis. Guidelines for effective antibiotic therapy include [100]:

- Establish an accurate clinical and laboratory diagnosis
- Select an appropriate antibiotic to which the organism is sensitive
- Select the least toxic antibiotic drug
- Establish adequate drug levels at the site of infection (minimum inhibitory concentrations - MICs)
- Frequent dosage strategy never taper to below qid
- Prescribe treatment for an appropriate length of time
- Augment drug therapy with physical procedures

**Table 56:** Topical antibiotics in South Africa [100]

| Flouroquinolones | | | |
|---|---|---|---|
| Ciloxan & Foxin | Ciprofoxacin 0.3% | Alcon / Genop | Sol/ung |
| Exocin & Octin | Ofloxaxin 0.3% | Allergan / Cipla | Solution |
| Okacyn | Lomefloxacin 0.5% | Norvartis | Solution |
| Vigamox | Moxifloxaxin 0.5% | Alcon | Solution |
| Zymar | Gatifloxacin 0.3% | Allergan | Solution |
| Aminoglycosides | | | |
| Tobrex & generic | Tobramycin 0.3% | Alcon | Sol/ung |
| Others | | | |
| Chloroptic / Chloramex | Chloramphenicol 5.0 mg/ml | Allergan | Sol/ung |
| Brolene | Propamidine isethionate 1.0 mg/ml | Allergan | Sol/ung |
| Spersamide | Sodium sulphacetamide 10 g | Norvartis | solution |
| Spersanicol | Chloramphenicol 0.5 g | Norvartis | Sol/ung |
| Fucithalmic | Fucidic acid | Al Pharm | ung |

**Table 57:** Antibiotic antimicrobial effective spectrum [100]

| | **Gram +** | | | | | **Gram -** | | | | | | | **Chlamydial** | **Amoebic** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Drug** | Staph. Aureus | Staph. Epidermidis | Strep. Pneumonia | Strep. Pyogenes | Corynobac. diphteriae | Heamophilus influenzae | Nesseria gonorrhoea | Escheichiae coli | Pseudomanas aeruginosa | Proteus mirabilis | Moraxella lacunata | Moraxella catarrhalis | Chlamidia trachomatis | **Acanthamoeba castellanii** |
| **Chloramphenicol, genrecis.** | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | | ++ | ++ | ++ | ++ | |
| **Spersamide** | ? | ? | ? | ? | ? | + | | | | | + | + | + | |
| **Neosporin** | + | + | + | + | + | + | + | ++ | + | + | ++ | ++ | | |
| **Brolene sol** | + | + | + | + | | | | | | | | | | **+** |
| **Brolene ung** | + | + | + | + | | | | + | ? | + | | | | **+** |
| **Tobrex** | + | + | | | | + | | + | +++ | | ? | ? | | |
| **Fucithalmic** | +++ MRSA | + | | | + | | | | | | | | | |
| **Ciloxan** | ++ | ++ | + | + | ++ | ++ | ++ | ++ | +++ | ++ | ++ | ++ | ++ | |
| **Ockacyn** | ++ | ++ | + | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | |
| **Exocin / Octin** | ++ | ++ | + | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | |
| **Vigamox** | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | ++ | +++ | +++ | +++ | +++ | |
| **Zymar** | **+++** | **+++** | **+++** | **+++** | **+++** | **+++** | **+++** | **+++** | **++** | **+++** | **+++** | **+++** | **+++** | |

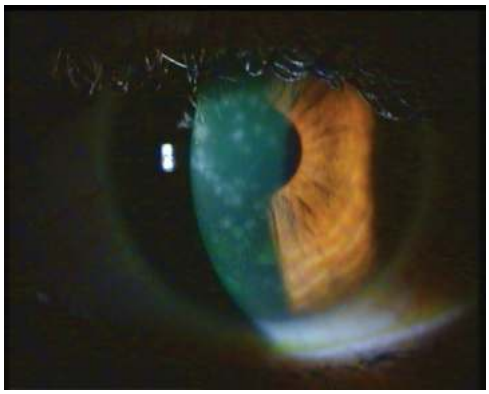

**Figure 105:** Sub-epithelial infiltrates from epidemic keratoconjunctivitis caused by an adenoviral infection

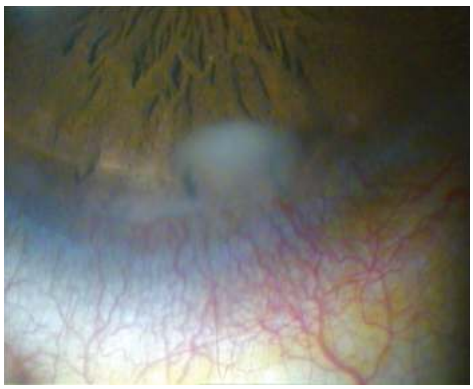

**Figure 106:** Peripheral infiltrate, there is no evidence of staining therefore it can be classified as sterile

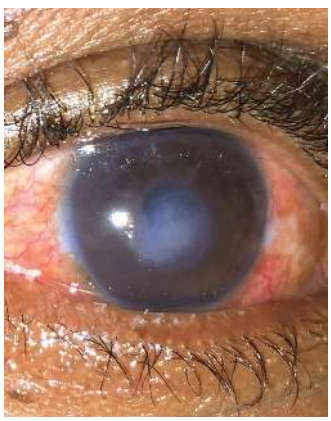

**Figure 107:** Central corneal infiltrative keratitis likely caused by pseudomonas aeruginosa

## CORNEAL ENDOTHELIAL COMPLICATIONS

### Endothelial Bedewing

McMonnies and Zantos, 1979 described the appearance of deposits on the endothelium of patients that were intolerant to contact lens wear. They coined the term "endothelial bedewing" [458]. Endothelial bedewing is characterised by the appearance of small inclusions in the region of the inferior cornea near or immediately below the inferior pupil margin, at the level of the endothelium. The condition is usually bilateral [458]. The best way to observe the bedewing is by marginal retro-illumination. Using this technique, the inclusions appear as bright

circular optically translucent entities, displaying "reversed illumination", which means that the distribution of light within the inclusion is opposite to the background distribution of light. When viewed in direct illumination, bedewing appears as fine white precipitates or an orange-brown dusting of cells. The colour is often an indicator of the time the inclusions have been present, newly deposited cells are usually white becoming pigmented over time [21]. The main feature associated with endothelial bedewing is intolerance to contact lens wear and mild conjunctival redness. Other signs are epithelial erosions and epithelial oedema with reduced corneal transparency. The entrapped material has a higher refractive index than the surrounding tissue resulting in the reversed illumination. Inclusions are most likely inflammatory cells embedded between the endothelium cells. This suggests an inflammatory aetiology for bedewing, most probably a mild anterior uveal inflammation [459, 460]. It is postulated that hypoxia induces a release of prostaglandins and other inflammatory mediators from the corneal tissues. These mediators diffuse into the anterior chamber and aqueous initiating an inflammatory response from the iris tissue. Inflammatory cells are released into the aqueous, which eventually come to rest on the endothelium, where they make their way in between the endothelium cells – endothelial bedewing. It has also been postulated that a mild anterior uveal response unrelated to lens wear may develop causing lens intolerance, due to the inflammation of the eye [21] [459, 460].

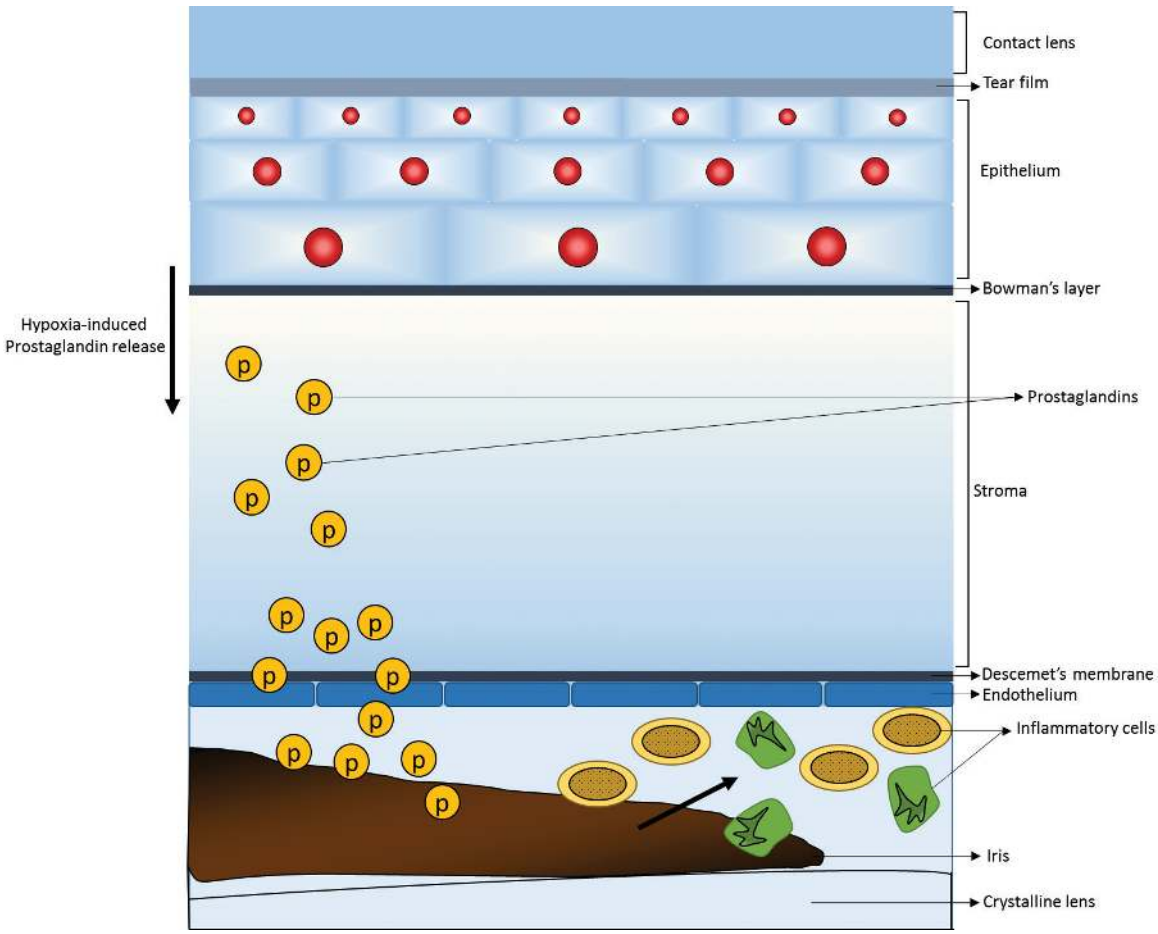


**Figure 108:** Proposed mechanism of endothelial bedewing.

Hypoxia induces a release of prostaglandins and other inflammatory mediators from the corneal tissues. These mediators diffuse into the anterior chamber and aqueous initiating an inflammatory response from the iris tissue. Inflammatory cells are released into the aqueous which, eventually come to rest on the endothelium, where they make their way in between the endothelium cells – endothelial bedewing.

**Management and Prognosis [21]**

- Reduce wearing time
- Check for concurrent pathology - uveitis
- Check for raised intraocular pressure, due to inflammatory cell migrating into anterior angle creating a blockage of aqueous outflow. Perform gonioscopy if IOP is elevated
- Medical treatment may be indicated in severe cases to resolve the uveitis

Lens intolerance can persist for many months even after the bedewing has disappeared. Bedewing can take months rather than weeks to resolve.

### Endothelial Blebs

Zantos and Holden, 1977 noticed that the corneal endothelial mosaic undergoes a dramatic alteration in appearance within minutes of inserting a contact lens. They observed several black, non-reflecting areas in the endothelial mosaic, appearing to increase the separation between the cells. They coined the term "endothelial blebs". The blebs can be observed under high magnification using specular reflection with a slit lamp [461]. The prevalence of endothelial blebs is essentially 100% amongst contact lens wearers – blebs can be observed within 10 minutes of lens insertion. The blebs appear as black, non-reflecting areas in the endothelial mosaic, giving the impression that individual cells have fallen off the posterior surface of the cornea, leaving behind holes or gaps in the endothelial layer [461]. The number of blebs peak within 20–30 minutes and the response subsides within 45–60 minutes to a low level response, which can be observed throughout the wearing period [461]. Vannas et al., 1981 described the blebbed cell as having a posterior bulge (toward the area of least resistance) caused by oedema of the nuclear area of the cell, intracellular vacuoles and fluid spaces between the cells [459]. With confocal microscopy the bleb appears to have a bright centre spot surrounded by a dark annulus, due to the light reflected away from the objective by the bulged posterior surface of the cell. The aetiology of blebs was explained by Holden et al., 1985 who concluded that a local acidic pH change in the endothelium caused by an increase in carbonic acid, due to hypercapnia and increased levels of lactic acid caused by lens induced hypoxia was the cause of endothelial blebs [460]. Blebs occur mainly with hydrogel soft lenses, less commonly with RGPs and are not seen with silicone hydrogel lenses due to the high oxygen permeability of these lenses.

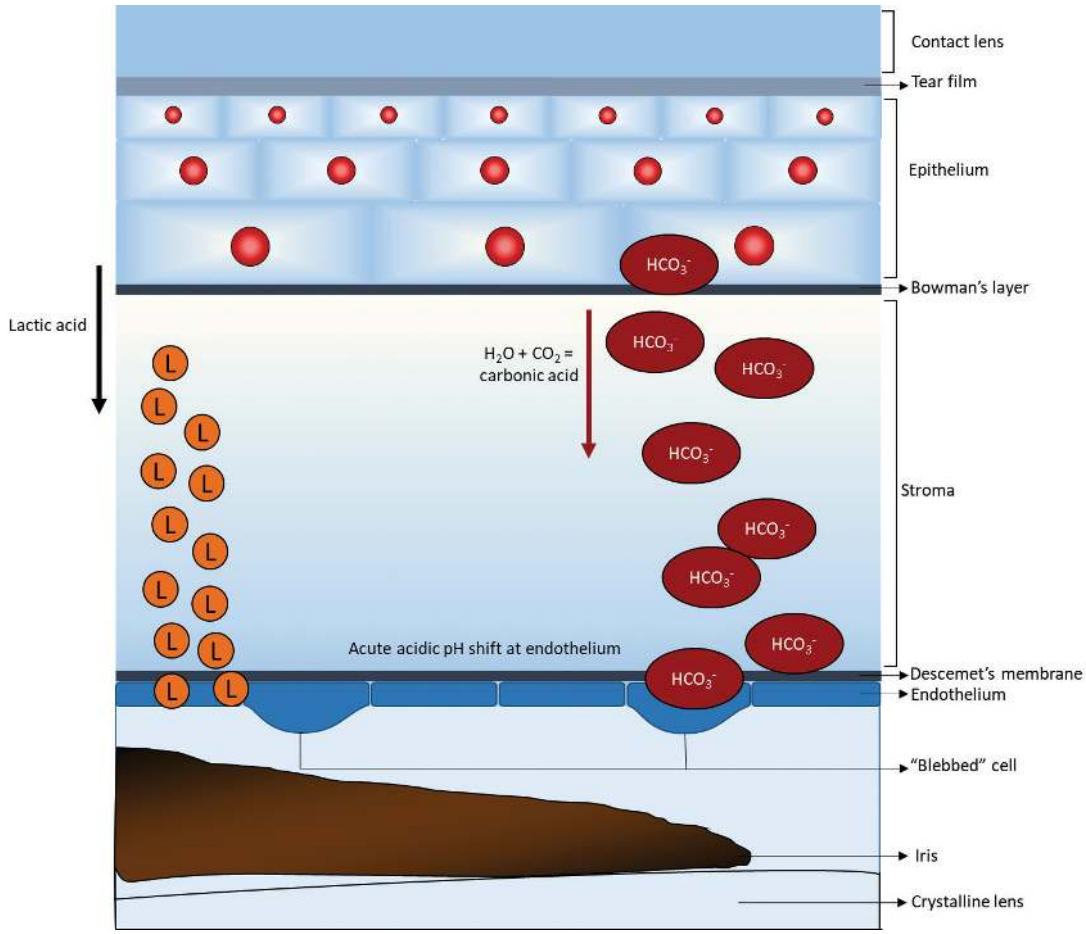


**Figure 109:** Proposed mechanism of endothelial bleb formation

A local acidic pH change in the endothelium caused by an increase in carbonic acid, due to hypercapnia and increased levels of lactic acid caused by lens induced hypoxia is the cause of endothelial blebs.

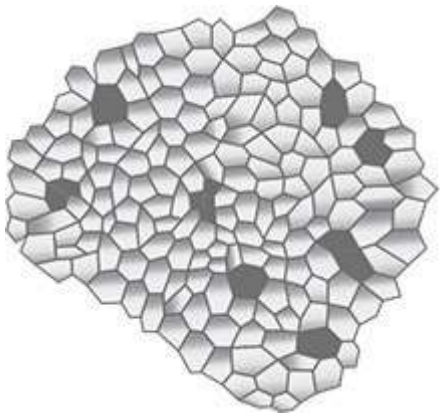

**Figure 110:** Endothelial blebs seen with the slit lamp biomicroscope

## Management and Prognosis

Although patients are unaware of blebs, the bleb response may indicate that the endothelium has lost its capacity to respond to changes in its immediate environment. Blebs may be linked to polymegethism, the later thought to be a long term adaptation to the bleb response [21]. Patients with a bleb response should be refitted with high Dk/t

silicone hydrogel lenses. The prognosis for recovery from endothelial blebs is excellent. After removal of the contact lenses the blebs will disappear within minutes, but they will recur within minutes, when lenses are reintroduced. Blebs seem to be harmless.

## Endothelial Polymegethism

### Terminology

#### *Polymegethism*

This term is derived from the Greek: 'megethos' – 'size' and 'poly' – 'many' and refers to increased variation in cell size [120].

#### *Pleomorphism*

This term refers to a decrease in the frequency of hexagonal cells or different cell shapes. Individual endothelial cells can have from three to nine sides, although the majority of the cells in the normal endothelium have six sides [120].

#### *Polymorphism*

This term refers to many shapes or variation in endothelial cell shapes [120].

#### *Polygonality*

Refers to the multiple sides forming the cell [120].

Contact lenses may induce short-term and long-term corneal endothelial changes. The endothelial bleb response is a short-term, reversible change noted with contact lens wear. Long-term endothelial changes such as polymegethism (increased variation in cell size) and pleomorphism (a decrease in the frequency of hexagonal cells) have also been detected in polymethylmethacrylate, rigid gas permeable and daily and extended wear soft contact lens patients. These morphometric changes have also been seen in myopes, aphakes and corneal transplant recipients. Differences in endothelial morphometry between the central and mid-peripheral regions of the cornea have also been noted in hard lens wearers [462]. Wiffen et al., 2000 confirmed that there is no endothelial cell loss with contact lens wear, but that the endothelial cells are redistributed from the centre of the cornea too the mid-periphery of the cornea with no net change in the endothelial cell density of the entire cornea [463]. Endothelial polymegethism is a natural age change that occurs in all humans, contact lenses have the effect of accelerating such changes. Lenses of extremely high oxygen permeability (silicone hydrogel) do not seem to accelerate these changes, which indicate that some measure of hypoxic stress induce a degree of polymegethism and polymorphism [21]. In the normal endothelium of a young adult, the endothelium displays a low degree of polymegethism, the ratio of the smallest cell to the largest cell that can be seen is around 1:5. In advanced cases of polymegethism this ration can increase to 1:20.

According to Bergmanson, 1992 the normal corneal endothelium shows considerable interdigitation of lateral cell sides oriented normal to the endothelial surface with minimal separation between cells. Acute anterior corneal hypoxia leads to filling of potential spaces between cells, straightening the interdigitated lateral cell walls, orienting them obliquely. Chronic anterior corneal hypoxia causes an oblique reorientation of cell walls, smaller anterior cell surfaces and larger posterior surfaces. This means that the shape of the endothelial cells has changed, but their volume has remained constant. Observing the anterior surface of the cells on specular reflection, it seems that the cells sizes differ considerably, while the cells have merely become reoriented in three-dimensional space. Bergmanson, 1992 also found that although the cells showed some inter and intracellular oedema, they were otherwise healthy and contained normal organelles. He suggests that polymegethism is a non-problematic adaptation to chronic metabolic stress [349]. The aetiology of endothelial polymegethism is similar to that of endothelial blebs, polymegethism

represents a chronic adaptation and blebs an acute response to the same stimuli. Blebs and polymegethism occur mainly with hydrogel soft lenses, less commonly with RGPs and are not seen with silicone hydrogel lenses due to the high oxygen permeability of these lenses. It seems that the increased carbonic and lactic acid may cause an acidic shift in the pH of the extracellular fluid surrounding the endothelial cells. This may induce changes in the membrane permeability/ or membrane pump activity that result in fluid movement into the cells, resulting in the elongation of cell walls and changes in cell shape, to preserve cell volume.

**Management and Prognosis**

The general strategy is to alleviate acidosis by using higher Dk/t lens materials, such as silicone hydrogels or RGP lenses. Lens thickness can be reduced, as well as wearing time (no extended wear) and changing to daily disposable lenses. The recovery from polymegethism is poor. After cessation of wear of high water content lenses on an extended wear basis for a 5-year period, Holden et al., 1985 were unable to detect a recovery. This was corroborated by other authors, and therefore the conclusion is that endothelial polymegethism induced by contact lenses is essentially a permanent change unlikely to change back to age-related normality [462, 464, 465].

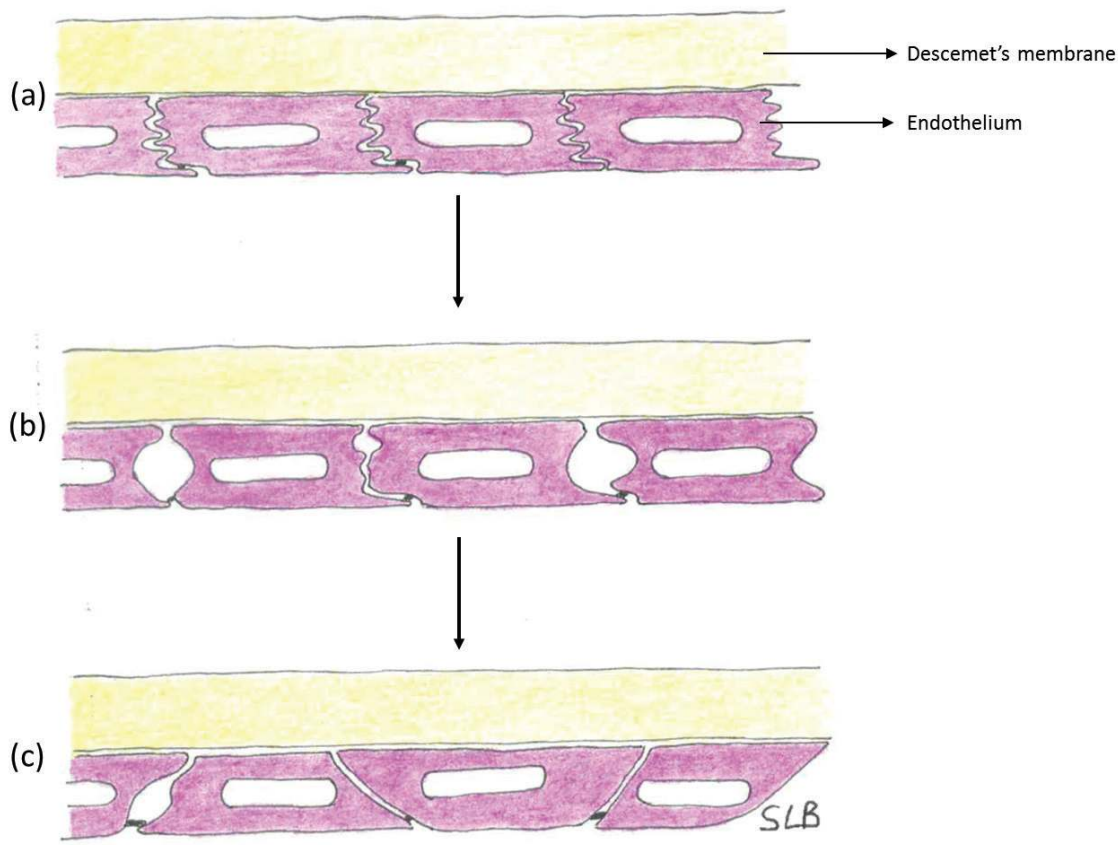


**Figure 111:** Mechanism of endothelial polymegethism

The normal endothelium shows considerable interdigitation of the lateral sides and minimal separation between cells (a). Acute anterior hypoxia causes a water imbalance that leads to the filling up of potential spaces between the endothelial cells. The result is a straitening of the interdigitated lateral walls of the cells (b). Chronic anterior hypoxia causes an oblique reorientation of the lateral cell walls. The cells now have a smaller posterior surface and larger anterior surface. The volume of the cells remains the same despite the variation in surface area (c).

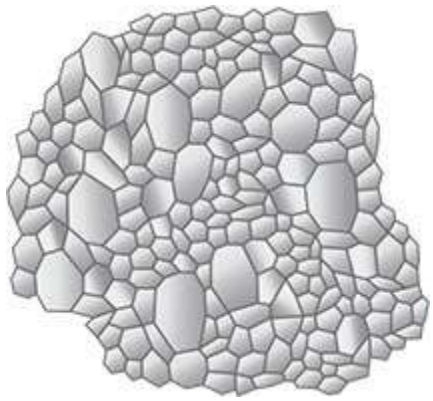

**Figure 112:** Endothelial polymegethism seen with the slit lamp biomicroscope

**Table 58:** Major contact lens complications and their aetiology

| Complications | Infectious | Immunological | Mechanical | Physiological | Other |
|---|---|---|---|---|---|
| **Bedewing** | | | X | X | |
| **Cells or flare** | X | X | X | | |
| **Conjunctival hyperaemia** | X | X | X | X | X |
| **Endothelial changes** | | | | X | |
| **Epithelial breakdown** | X | X | X | X | |
| **GPC** | | X | X | | |
| **Keratoconjunctivitis** | X | X | | X | X |
| **Limbal engorgement** | | | X | X | |
| **Microcystic edema** | | | X | X | |
| **Microcysts** | | | X | X | X |
| **Mucus / debris build-up** | | X | X | | X |
| **Neovascularisation** | X | X | X | X | |
| **Pannus** | X | X | X | X | |
| **Pseudo dendrites** | X | X | | X | |
| **Stippling** | | | X | | X |
| **Striate Keratitis** | X | | | X | X |
| **Stromal oedema** | X | | X | X | X |
| **Stromal infiltrates** | X | X | | | |
| **Sub epithelial infiltrates** | X | X | | | |
| **SPK** | X | X | X | X | X |
| **SLK** | | X | X | | X |
| **Toxic keratitis** | X | X | | | X |
| **Ulceration** | X | X | X | X | |