Uveitis

Uveitis is inflammation of the uveal tract, with or without inflammation of neighbouring structures (e.g., the retina or vitreous). The term covers a diverse group of conditions leading to the common endpoint of intraocular inflammation, and which have been estimated to cause approximately 10% of severe visual impairment. This makes uveitis one of the leading causes of preventable severe visual loss in developed countries.[1]

See separate Chorioretinal Inflammation and Choroidal Disorders articles for additional detail on posterior uveitis.

Anatomy of the uveal tract

The uveal tract is the pigmented middle layer of the three concentric layers that make up the eye, lying between the sclera (superficial to it) and the retina (deep to it). It consists of the iris, ciliary body and choroid. The name comes from the Latin uva, meaning grape; it is possibly a reference to its purplish colour, wrinkled appearance and grape-like size and shape.

Classification of uveitis[2, 3]

Anatomical

Uveitis may be unilateral or bilateral. It is classified by anatomical location of the inflammation, by inflammatory appearance and by chronicity:

- Unilateral conditions are more commonly acute and can be infectious.
- Bilateral conditions are likely due to chronic, systemic conditions.

Uveitis may be anterior, intermediate, posterior or panuveitis. More anatomically descriptive terms have been used in the past and persist in scientific literature and usage.

- Anterior uveitis describes inflammation of the iris. It is also referred to as iritis, iridocyclitis (if there is also ciliary body involvement) or anterior cyclitis (if only the anterior portion of the ciliary body is affected).
- Intermediate uveitis affects the vitreous and posterior part of the ciliary body. It is also referred to as pars planitis or posterior cyclitis, or as hyalitis when the inflammation involves only the anterior portion of the vitreous.
- Posterior uveitis describes inflammation of the choroid. It is also referred to as choroiditis, or as chorioretinitis if the retina is also involved. It may also affect the retinal blood vessels, giving rise to retinal vasculitis. Posterior uveitis is further defined as being focal, multifocal or diffuse, depending on the nature of the inflammatory lesions seen on the fundus.
- Panuveitis describes inflammation throughout the uveal tract.
By duration and course\textsuperscript{[4]}
- Acute conditions typically have an abrupt onset lasting several weeks. If left untreated, an acute condition can develop into a chronic cellular response.
- Chronic uveitis is active uveitis that persists longer than three months. It is associated with a high incidence of vision-threatening complications, such as cataract, macular oedema and glaucoma, which may cause irreversible visual loss.\textsuperscript{[5]}

Granulomatous inflammation vs non-granulomatous\textsuperscript{[6]}
Keratic precipitates (KPs) are clusters of white blood cells found on the posterior (endothelial) part of the cornea, resembling little white spots. Those which are larger and greasy-looking are referred to as mutton-fat KPs. Uveitis is classified by the morphology of the KPs into non-granulomatous (small KPs) and granulomatous (mutton-fat KPs):
- Non-granulomatous uveitis is more common. It is usually anterior and has an acute onset accompanied by a cellular reaction in the anterior chamber, involving smaller cell types (lymphocytes) than those in granulomatous inflammation. It is most commonly idiopathic or due to HLA-B27 involvement.
- Granulomatous uveitis is usually chronic. There are large inflammatory cells in the anterior chamber. It is often associated with systemic conditions and autoimmune reaction, or arises from the host's immune response to a systemic infectious process, such as syphilis, Lyme disease, tuberculosis or herpetic viral infection.

Aetiology
The various forms of uveitis represent the common end result of multiple underlying causes of ocular inflammation. These include:\textsuperscript{[2]}
- Inflammatory - due to autoimmune disease.
- Infectious - caused by known ocular and systemic pathogens.
- Infiltrative - secondary to invasive neoplastic processes (sometimes referred to as masquerade syndromes). Intraocular lymphoma may present as a chronic uveitis in older patients. Intraocular tumours may also occasionally present with posterior uveitis.
- Trauma - a common cause of anterior uveitis. Sympathetic ophthalmitis (sometimes referred to as sympathetic ophthalmitis) is a rare form of bilateral panuveitis in response to trauma or surgery to one of the eyes. See also separate Sympathetic Ophthalmia article.
- Iatrogenic - caused by surgery, inadvertent trauma, or medication (eg, rifabutin, cidofovir).
- Inherited - secondary to metabolic or dystrophic disease.
- Ischaemic - caused by impaired circulation.
- Idiopathic - when evaluation has failed to find an underlying cause. Most uveitis, particularly anterior uveitis, is idiopathic.
- Immunosuppression causes a particular risk of infection-related uveitis.
In Britain, sarcoidosis is the most common systemic disease that presents as chronic uveitis. In Japan, Behçet’s disease is the most common systemic disease associated with chronic uveitis and, in other parts of the world, it may be tuberculosis.

Some ocular syndromes can give rise to anterior or posterior uveitis.\[7\]

**Pathophysiology**\[2, 8\]

Uveitis is the eye’s response to a wide range of intraocular inflammatory diseases of infectious, traumatic, genetic or autoimmune aetiology. The end pathology results from the presence of inflammatory cells and the sustained production of cytotoxic cytokines and other immune regulatory proteins in the eye.

- Trauma-related uveitis may result from a combination of microbial contamination and accumulation of necrotic products at the site of injury, stimulating an inflammatory response.
- Infection-related uveitis may produce inflammation through the immune reaction directed against foreign antigens, which injure the uveal tract vessels and cells.
- Autoimmune uveitis may result from immune complex deposition within the uveal tract.

In one 1996 study of 1,230 patients in the USA the distribution in aetiology was as follows:\[9\]

- Idiopathic (34%).
- Seronegative spondyloarthropathies (10.4%).
- Sarcoidosis (9.6%).
- Juvenile rheumatoid arthritis (JRA) (5.6%).
- Systemic lupus erythematosus (4.8%).
- Behçet’s disease (2.5%).
- HIV/AIDS (2.4%).

**Epidemiology**\[1, 4, 6\]

- Anterior uveitis is the most common form in the UK.
- The prevalence of uveitis is variously given as 25-50 per 100,000 persons, with the mean onset at 30.7 years of age.
- Most people who develop uveitis are aged 20-50 years.
- Roughly 5% to 10% of these cases occur in children under the age of 16.
- The epidemiology of uveitis varies with geographical location. Finland has one of the highest incidences of uveitis and this is thought to be because of the high frequency of HLA-B27 spondylopathy amongst the population.
- Racial predisposition is related to the patient’s underlying systemic disease (eg, HLA-B27 positivity in Caucasians, Behçet’s disease in individuals of Mediterranean origin).

The prevalence of each underlying aetiology varies with age group, race and gender. For example:

- Children: juvenile rheumatoid arthritis, toxocariasis.
- Males: ankylosing spondylitis, reactive arthritis (Reiter’s syndrome), Behçet’s disease, sympathetic ophthalmia.
- Females: Rheumatoid arthritis, juvenile rheumatoid arthritis.

**Presentation**\[4, 10, 11\]

Clinical features vary depending on the location of the inflammation. Symptoms may develop over hours or days (acute uveitis), or onset may be gradual (chronic uveitis).

**Symptoms**\[11\]

**Acute anterior uveitis**

- Usually unilateral.
- Pain, redness and photophobia are typical.
- Eye pain is often worse when trying to read.
- Progressive - occurs over a few hours/days.
- Blurred vision.
- There may be excess tear production.
- Associated headache is common.
- Not all symptoms may be present at the start of an attack.

**Chronic anterior uveitis**

- Recurrent episodes, with less acute symptoms.
- Blurred vision and mild redness are common, often with little pain or photophobia, except during an acute episode.
Patients may find that one symptom predominates (typically this is blurred vision). They tend to become good at spotting this early.

**Intermediate uveitis**

- Painless floaters and decreased vision (as for posterior uveitis).
- Minimal external signs of inflammation (such as redness or pain).

**Posterior uveitis**

- Gradual visual loss.
- Usually bilateral.
- Blurred vision and floaters.
- Occasional photophobia; however, general absence of anterior symptoms (pain, redness and photophobia).
- The presence of symptoms of posterior uveitis WITH pain suggests:
  - Anterior chamber involvement (panuveitis).
  - Bacterial endophthalmitis.
  - Posterior scleritis.
  - Orbital inflammatory disease.

- Sudden bilateral loss of vision suggests VKH syndrome or sympathetic ophthalmia.

**Panuveitis**

Presents with any combination of the above symptoms.

**NB:** some types of uveitis are more insidious and may be asymptomatic (eg, that associated with juvenile idiopathic arthritis).

**Examination**

Fully dilated eye examination, including slit-lamp examination, is required to look for signs of posterior disease. The structures of the eye should be examined for diagnostic features and for features which may point to the underlying cause. Intraocular pressures (IOPs) should also be checked.

**Visual acuity**

Should be checked, may be reduced and, if so, is an important factor in management.
External eye

- Lids, lashes and lacrimal ducts are normal.
- Conjunctiva: typically 360° perilimbal injection, more intense close to the limbus; this is the reverse of the pattern seen in conjunctivitis, in which the most severe inflammation occurs further from the limbus.
- Visual acuity may be decreased.
- Extraocular movement: generally normal.

Pupils

- There may be direct photophobia
- There may be consensual photophobia (typical of iritis: photophobia due to more superficial causes is typically direct but not consensual).
- Miosis is common.

Epithelium and stroma

Look for abrasions, oedema, ulcers, foreign bodies.

Cornea

Look for:

- KPs - inflammatory cells clumped together on the posterior (endothelial) part of the cornea as little white spots. KPs are characteristic of uveitis. When KPs appear large and granular or greasy, the uveitis is described as granulomatous.
- Ciliary flush, a violaceous ring around the cornea, suggests intraocular inflammation.
- Corneal oedema may be seen.

Lens

Lens changes may occur, most commonly posterior subcapsular opacity secondary to steroid use. These are not specific for uveitis.

Anterior chamber

- In uveitis, severely inflamed vessels leak protein which clouds the normally clear aqueous. This looks hazy with the slit lamp. If severe, it disperses the light beam, causing flare.
- White or red blood cells may be observed: the presence of inflammatory cells in the anterior chamber suggests inflammation of the iris and ciliary body.
- Blood cells: grading of blood cells in the anterior chamber is as follows:
  - 0 - None.
  - 1+ - faint (barely detectable).
  - 2+ - moderate (clear iris and lens details).
  - 3+ - moderate (hazy iris and lens details).
  - 4+ - intense (fibrin deposits, coagulated aqueous).
- Hypopyon may be present if there is significant inflammation. This is highly suggestive of diseases associated with HLA-B27, Behçet’s disease or, less commonly, infectious uveitis.

Iris

- There may be anterior or posterior synechiae on the iris as a result of inflammation. These have the potential to lead to secondary glaucoma.
- Iris atrophy is a diagnostic feature of herpetic uveitis. Herpes simplex causes diffuse atrophy while herpes zoster typically causes sectoral atrophy.
- Iris nodules may be seen in sarcoidosis, tuberculosis, VKH syndrome, sympathetic ophthalmia and syphilis.
Vitreous
Inflammatory cells in the vitreous, which may be clumped, suggest posterior disease.

Retina and macula
- Associated retinitis causes a yellow-white appearance and poorly defined edges, often associated with haemorrhage and exudation.
- Retinal vasculitis is usually seen in retinitis and may be seen in granulomatosis with polyangiitis (Wegener’s granulomatosis), systemic lupus erythematosus, and viral retinitis including herpetic infections.
- Inflammation may lead to cystoid macular oedema, neovascularisation and macular holes.

Optic disc
- Disc inflammation can occur even without other signs of uveitis. It usually appears as papillitis or disc oedema, neovascularisation, infiltration and cupping.
- Sarcoidosis and leukaemia can infiltrate the disc tissue, producing an appearance similar to papillitis.

IOP
IOP is most often decreased owing to impaired production of aqueous by the non-pigmented ciliary body epithelium. However, in some infective conditions (eg, herpetic uveitis, toxoplasmosis) it is increased due to the accumulation of inflammatory material and debris in the trabecular meshwork, trabeculitis, obstruction of venous return, and steroid therapy.

NB: if the history or examination suggests systemic symptoms, a further full physical examination is needed. [4, 7]

Examination findings by anatomical type

Anterior uveitis
- Visual acuity is often reduced.
- The pupil may be abnormally shaped or of a different size to the unaffected eye.
- Direct photophobia and consensual photophobia (pain on shining a light into the unaffected eye) may be demonstrated.
- Circumlimbal injection (injection around the corneal limbus) is characteristic. This can be fairly localised but, as the uveitis progresses, the entire conjunctiva may appear red.
- The main signs are seen in the anterior chamber:
  - The characteristic sign is the presence of cells in the aqueous humour. As you shine the slit-lamp beam through the anterior chamber, the appearance is of a shaft of light shining through darkness with bits of dust floating through it.
  - The severity of the uveitis is graded by the number of cells seen, ranging from 0 (no cells seen) to +4 (>50 cells seen).
  - The aqueous humour may become cloudy, with ‘flare’. This appears rather like a shaft of light shining through a darkened, smoky room. Flare is graded from 0 (no flare) to +4 (fibrin deposition).
  - Other findings may include synechiae and keratic precipitates.

Intermediate uveitis
- Intermediate uveitis involves the anterior vitreous, ciliary body and peripheral retina.
- Inflammatory cells in the vitreous are best seen with a slit lamp in the dilated eye.
- Pars planitis refers to a subset of intermediate uveitis where clumps of white cells form globular yellow-white ‘snowballs’ in the inferior peripheral vitreous, and yellow-white exudates, band to form ‘snowbanks’.

Examination findings by anatomical type

Intermediate uveitis
**Posterior uveitis**

- Inflammatory lesions may be seen on the retina or choroid. They may look yellow when fresh; older ones have a more distinct edge and a whitish appearance.
- Inflammation of the retinal blood vessels (retinal vasculitis) may occur.
- Oedema of the optic nerve may occur.
- The inflammation may ‘spill over’ anteriorly so that there are inflammatory cells in the vitreous.

**Scoring systems in uveitis**

Various systems based on scoring a number of presenting clinical features have been proposed to assist in diagnosis and to standardise research findings. These include:

- Location of inflammation.
- Anterior chamber cells.
- Anterior chamber flare.
- Vitreous cells (present or absent).
- Vitreous haze.

**Differential diagnosis**

Any cause of a red eye or visual disturbance should be included in the differential diagnosis.

**Investigations**

A first episode of mild, unilateral non-granulomatous acute uveitis can be diagnosed by history and clinical examination alone. Laboratory investigation is not usually helpful if there is trauma or a known systemic disease, or if the history and examination do not suggest systemic disease.

- Imaging may be helpful where there is posterior disease, in order to assess site or severity of posterior inflammation. Fundus fluorescein angiography and optical coherence tomography (OCT) are the commonly used techniques.

If history and examination are normal but the uveitis is granulomatous, recurrent or bilateral, further investigations are necessary to look for underlying causes. The exact nature of the investigation is guided by clinical suspicion. Investigations might include:

- FBC.
- ESR.
- Antinuclear antibody.
- Angiotensin-converting enzyme.
- Rapid plasma reagin.
- HLA testing.
- Mantoux test.
- CXR (to exclude sarcoidosis or tuberculosis).
- Urinalysis
- Infectious workup (eg, depending on presentation, toxoplasma, Lyme disease, HIV, VDRL).
- Laboratory tests on a sample of aqueous or vitreous may be helpful where infection or malignancy is suspected.

**Associated diseases**

- About 50% of cases of uveitis are idiopathic.
- About 50% of patients with acute anterior uveitis are HLA-B27-positive.
- Some infections are specifically associated with anterior uveitis, including herpes simplex and herpes zoster.

Common associations are listed here: fuller lists can be obtained in the ‘Further reading & references’ section, below.

**Non-granulomatous disease**

This is associated with:

- Sacrolitis.
- Seronegative arthropathies:
  - Ankylosing spondylitis
  - Reactive arthritis (Reiter’s syndrome)
  - Psoriasis
- Inflammatory bowel disease
- Early sarcoidosis
- Early tuberculosis
- Behçet’s disease
- Juvenile idiopathic arthritis
- Early syphilis
- Leptospirosis
- Drug-induced uveitis
- Traumatic uveitis

**Granulomatous anterior and posterior uveitis**
These are associated with:

- Sarcoidosis
- Toxoplasmosis
- Cytomegalovirus
- Herpes simplex virus
- Herpes zoster virus
- Tuberculosis
- Syphilis
- In AIDS:
  - Cytomegalovirus
  - Human syncytial virus
  - Cryptococcosis
  - Candidiasis

**Non-infectious causes of posterior disease**
These include:

- Behçet's disease.
- Sacroiliitis (usually bilateral).
- Lymphoma.
- VKH syndrome.
- Lens-induced uveitis.
- Posterior uveitis - may also be associated with autoimmune retinal vasculitis.

**Management**[4, 5, 10]

Refer people with suspected uveitis to an ophthalmologist within 24 hours. Do not initiate treatment for recurrent uveitis in primary care, unless asked to do so by an ophthalmologist: delay in appropriate management can lead to the development of significant complications and irreversible loss of vision.

The aims of treatment are to control inflammation, prevent visual loss and minimise long-term complications of the disease and its treatment. There is no standard regimen: treatment is determined by the type of uveitis, whether it is secondary to infection and whether it is likely to threaten sight. Systemic drugs are reserved for sight-threatening posterior disease.
All patients with anterior disease and most with intermediate or posterior disease require treatment.

In chronic uveitis, treatment is usually indicated if the visual acuity has fallen to less than 6/12, or if the patient is experiencing visual difficulties.

Cycloplegic drugs
Cycloplegic-mydriatic drugs (eg, cyclopentolate 1%) are used to paralyse the ciliary body. This relieves pain and prevents adhesions between the iris and lens.

Steroids
- Corticosteroids are used to reduce inflammation and prevent adhesions in the eye. They may be given topically, orally, intravenously, intramuscularly, or by periocular or intraocular injection, depending on the severity of the uveitis. Corticosteroids are reduced slowly, as withdrawing them too quickly may lead to rebound inflammation.
- Many patients with unilateral chronic uveitis can be managed with topical corticosteroids, with periocular corticosteroids for macular oedema and visual loss.
- Systemic corticosteroids are the mainstay of systemic treatment for patients with chronic uveitis: the usual indication for treatment is the presence of macular oedema and visual acuity of less than 6/12.

Immunosuppressors
- Cyclosporin is the drug of choice for most patients aged under 50 years.
- Ciclosporin and tacrolimus have been shown to be associated with control of ocular inflammation and preservation or restoration of sight. However, currently immunosuppressive treatment is not licensed for uveitis.
- Other agents such as mycophenolate, tacrolimus and humanised Tac monoclonal antibodies have been used.
- The decision to start treatment with immunosuppressive drugs is a long-term commitment by both the clinician and patient, as treatment is likely to last for a minimum of six months and is often much longer.

Adjunctive therapy
- Infectious uveitis (bacterial, viral, fungal, or parasitic) is treated with an appropriate antimicrobial drug as well as corticosteroids and cycloplegics. [4] See also separate Chorioretinal Inflammation article.
- Severe or chronic uveitis may be treated with laser phototherapy, cryotherapy or vitrectomy.
- Biologics, which target mediators of the inflammation cascade, may offer the potential to provide more effective and less toxic treatment. [15]
- Ongoing research is examining the use of immune modulators such as tumour necrosis factor alpha-blockers (eg, etanercept, infliximab) and interleukin-2 receptor blockers.
  - Interferon alfa may also have potential in treating refractory sight-threatening uveitis from a variety of causes. [16]
  - Azathioprine has been found to be useful in steroid-resistant autoimmune uveitis. [17]
  - The antivascular endothelial growth factor drugs (eg, ranibizumab, Lucentis®) which are currently used for ‘wet’ age-related macular degeneration may have a role in managing chronic, non-infective uveitis but are not yet licensed for this use. [4] Intravitreal injection carries a small inherent risk of complications (including sight loss) in itself.
- Research is also focused on less invasive sustained ocular drug delivery systems, including episcleral implants, nanospheres and cyclodextrin particles. [18]

Considerations prior to initiating treatment
These include:
- Supporting evidence for specific treatments is sparse.
- IOP should be checked and herpes simplex virus keratitis ruled out before starting topical corticosteroids.
- Steroid treatment should only be initiated in consultation with an ophthalmologist.

Surgery
- Surgery is considered in a small proportion of patients with severe or intractable disease or where a diagnostic vitreous sample is required (eg, to diagnose infection or malignancy). [4]
- Surgery may also be required for complications such as cataract, glaucoma and vitreoretinal problems; however, except in emergency situations, it should be contemplated only once the uveitis is controlled, ideally for at least three months. [5]
- Vitrectomy may be helpful when there is substantial opacity but also may improve disease control, particularly in younger patients. [5]

Monitoring
Monitoring is mainly by clinical examination but some investigations provide a useful adjunct:
- OCT is helpful in looking for macular causes of worsening vision.
- Fluorescein angiography is helpful in assessing retinal vascular involvement.
- The only patient group currently screened for uveitis is children with juvenile idiopathic arthritis.
Complications

The main complication of uveitis is visual loss as a result of one or more of the following list (the first two being the leading causes):[6]

- Cystoid macular oedema.
- Secondary cataract.
- Acute rise in IOP, with or without glaucoma, either as a direct consequence of the inflammatory process or secondary to steroid treatment:
  - Some patients, especially those with a history of glaucoma, are prone to developing high IOP when on steroid treatment and require co-treatment to reduce it. Treatment can be stopped when the steroid treatment is stopped if there is no pre-existing glaucoma.

- Vitreous opacities (inflammatory debris or haemorrhage).
- Retinal detachment.
- Neovascularisation of the retina, optic nerve, or iris.
- Macular ischaemia, vascular occlusions and optic neuropathy - can be complications of posterior uveitis.

Posterior synchiae are a common complication of anterior uveitis; they can cause blockage of the aqueous flow, leading to a rise in IOP. They also complicate cataract surgery.

Prognosis

- Anterior uveitis can be a self-limiting condition. The factors determining which cases will resolve without intervention are unclear.
- With prompt and effective treatment, there is usually a good visual outcome (one study found that 91% of patients retain normal vision).[6]
- Relapse after a first episode of acute anterior uveitis is very common, particularly in patients aged 18-35 years. Recurrence rates as high as 66% have been reported, although there is a wide range in the number of reported attacks and the time period between them, which can be many years.[19]
- Newer treatments may offer improved outcomes for previously refractory cases.[21]
- The prognosis of chronic granulomatous uveitis depends on the cause and on how promptly any underlying condition is recognised and treated.

Further reading & references

10. Uveitis; NICE CKS, December 2014 (UK access only)

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