

Investigation and management of uveitis

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A full, much longer article, including several more images and web references, is on bmj.com.

Uveitis is estimated to account for 10% of blindness in people of working age in the Western world.¹ A retrospective review of patients attending a uveitis clinic in the United Kingdom found that 70% of patients had visual impairment (visual acuity 6/18 or worse) and half of these patients had bilateral visual impairment.² Acute anterior uveitis, which is the most common form of uveitis in the UK, usually has a good visual outcome, but other forms of uveitis have a poorer visual prognosis.

Uveitis is associated with many systemic diseases, including sarcoidosis, juvenile idiopathic arthritis, Behçet's syndrome, and infectious diseases such as tuberculosis. For patients with systemic disease a management approach that involves collaboration with other specialties is important. In about half of cases, no systemic association is found and uveitis is presumed to be autoimmune.³ The introduction of biological treatments for many autoimmune conditions, and intravitreal injection of drugs for some eye diseases, has led to several of these treatments being used in patients with uveitis, despite limited evidence from randomised trials to support their use. This review discusses recent advances in the diagnosis of uveitis, ocular imaging, and treatments. It does not cover uveitis induced by ocular surgery.

What is uveitis and who gets it?

Uveitis describes a group of intraocular inflammatory disorders that may be related to infection or are non-infective. The uvea comprises the iris, ciliary body, and choroid. Uveitis may affect other tissues in the eye, however, including the retina (uveoretinitis), retinal blood vessels (retinal vasculitis), the vitreous (vitritis), and the optic nerve (papillitis) (fig 1).

Uveitis affects people of any age, but most studies have found the highest prevalence in adults of working age.^{w1} Uveitis is defined by its anatomical location, onset, duration, and course. Box 1 outlines a classification of uveitis based on consensus from a recent expert working group. "Anterior uveitis" has replaced the terms iritis (inflamma-

SOURCES AND SELECTION CRITERIA

We searched the Cochrane Library using the terms "uveitis," "retinitis", "choroiditis", and "iritis". We also searched Medline using the same search terms, but limited the search to articles in English. We considered randomised controlled trials first, followed by prospective non-randomised trials and large retrospective case series. We reviewed "expert opinion" articles on topics where trial evidence was absent and also used our personal archives.

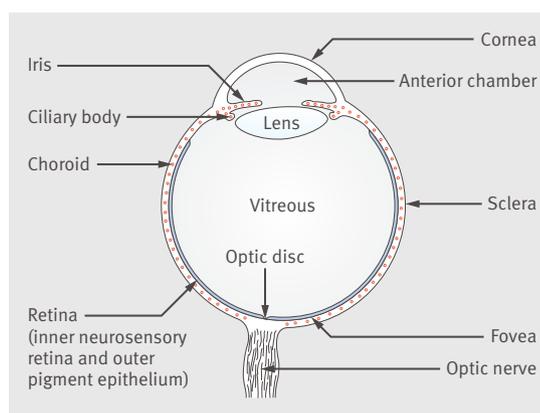


Fig 1 | Anatomy of the eye. The iris, ciliary body, and choroid form the uveal tract

tion of the iris) and "iridocyclitis" (inflammation of the iris and ciliary body).⁴

How does a patient with uveitis present?

Acute anterior uveitis typically presents with a painful, photophobic, red eye and blurred vision,^{w6} although patients may not have all these symptoms at the start of an attack. The predictive value of symptoms in diagnosing uveitis is unknown but photophobia is thought to be important, although it is not specific for uveitis as it is also prominent in corneal disease. A sticky or mucoid discharge is not found in uveitis (but is common in conjunctivitis).

Conjunctival injection (redness) in acute anterior uveitis starts, and is most intense, around the edge of the cornea (circumcorneal). In an eye with uveitis the pupil may be smaller than on the unaffected side as inflammation may trigger muscle spasm of the iris sphincter. Alternatively, the pupil may be distorted by posterior synechiae, which is where the iris adheres to the lens. The table lists other causes of red eye, along with their presenting features.

Other forms of uveitis can present in a similar way to acute anterior uveitis. Posterior uveitis, particularly, may

SUMMARY POINTS

- Uveitis is a major cause of visual impairment in people of working age
- Patients with suspected uveitis should have an assessment of visual acuity and a dilated slit lamp examination
- Children with juvenile idiopathic arthritis should be screened with regular slit lamp examinations to enable early detection and treatment of uveitis
- Optical coherence tomography is useful for detecting and monitoring cystoid macular oedema
- Intravitreal treatments and biological agents show promise in treating sight threatening non-infectious uveitis, but trial based evidence is limited

Box 1 | Standardised nomenclature for uveitis*

Anatomical

- Anterior—primary site of inflammation is the anterior chamber
- Intermediate—primary site of inflammation is the vitreous
- Posterior—primary site of inflammation is the retina or choroid
- Panuveitis—inflammation in anterior chamber and vitreous and retina or choroid

Onset

- Sudden or insidious

Duration

- Limited (≤3 months) or persistent (>3 months)

Course

- Acute—sudden onset and limited duration
- Recurrent—repeated episodes separated by periods of inactivity without treatment of ≥3 months' duration
- Chronic—persistent uveitis with relapse in <3 months after discontinuing treatment

*From the Standardization of Uveitis Nomenclature (SUN) Working Group⁴

be bilateral, and in such cases patients may present with white eyes and painless loss of vision. Floaters may be present if there is inflammation in the vitreous. Some types of uveitis, such as uveitis associated with juvenile idiopathic arthritis, are more insidious, and such patients are often asymptomatic.

What causes uveitis?

The cause of uveitis may be autoimmune, infection related, drug induced, traumatic, or associated with malignancy (when it is known as the masquerade syndrome). About half of cases are idiopathic and are presumed to be autoimmune.³ Box 2 shows some of the infectious causes and systemic disease associations.^{w7 w8} Some forms of chronic uveitis have characteristic features and are grouped together as uveitis entities—for example, birdshot chorioretinopathy.

The causes of uveitis vary around the world, which can be explained partly by genetic and environmental factors. In a prospective study of 865 patients in the Netherlands uveitis associated with HLA B27 but without systemic disease was the most common form of uveitis; sarcoidosis and seronegative spondyloarthropathies were the most common systemic associations; and toxoplasmosis was the most common infectious cause.³ Rates of infectious uveitis, particularly uveitis associated with tuberculosis, are higher in developing than developed countries.^{w14}

How do patients with uveitis lose vision?

Causes of vision loss in uveitis include cystoid macular oedema, cataract, secondary glaucoma, vitreous opacities

Box 2 | Infections and systemic diseases associated with uveitis

Anterior uveitis

Non-infectious

- Seronegative arthropathy
- Ankylosing spondylitis
- Reiter's syndrome
- Inflammatory bowel disease
- Juvenile idiopathic arthritis
- Sarcoidosis
- Behçet's syndrome

Infection related

- Herpes simplex virus
- Varicella zoster virus
- Tuberculosis
- Syphilis

Intermediate uveitis

Non-infectious

- Sarcoidosis
- Multiple sclerosis
- Lymphoma

Posterior uveitis and panuveitis

Non-infectious

- Sarcoidosis
- Behçet's syndrome
- Vogt-Koyanagi-Harada disease*
- Lymphoma

Infection related

- Toxoplasmosis
- Tuberculosis
- Cytomegalovirus
- Syphilis
- Toxocariasis
- Herpes simplex virus
- Varicella zoster virus
- Endogenous endophthalmitis

*A multisystem inflammatory condition of unknown cause affecting the eyes, auditory system, meninges, and skin

(inflammatory cell debris or vitreous haemorrhage), retinal vascular occlusions, chorioretinal scarring, inflammatory optic neuropathy, and retinal detachment.²

Cystoid macular oedema and secondary cataract are the leading causes of visual loss from uveitis in the UK and Europe.^{2 5} Cystoid macular oedema refers to the forma-

Differential diagnosis of red eye—typical presenting symptoms

	Pain	Reduced vision	Photophobia	Haloed	Discharge	Other
Acute anterior uveitis	Mild to moderate	Reduced or normal	Present	Rarely	Tearing or absent	
Acute glaucoma	Severe	Severely reduced	Present or absent	Present	Tearing or absent	Vomiting
Scleritis	Severe	Reduced or normal	Absent	Absent	Absent	
Episcleritis	Mild or absent	Normal	Absent	Absent	Absent	Gritty
Corneal ulcer bacterial	Moderate	Reduced or normal	Present	Absent	Purulent	
Herpes simplex keratitis	Moderate	Reduced or normal	Present	Absent	Watery	
Corneal erosion	Moderate	Reduced or normal	Present	Absent	Tearing	
Bacterial conjunctivitis	Absent	Normal	Absent	Absent	Purulent	Gritty
Viral conjunctivitis	Absent	Normal	Absent	Absent	Watery	Gritty
Allergic conjunctivitis	Absent	Normal	Absent	Absent	Mucoid or absent	Itch

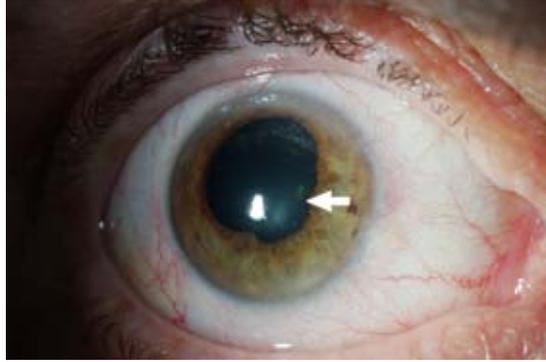


Fig 2 | Posterior synechiae. The iris adheres to the lens inferonasally (arrow), causing distortion of the (pharmacologically dilated) pupil. Posterior synechiae may not be apparent until the pupil is dilated. Pupil dilation will often break the synechiae

tion of one or more fluid filled cystoid spaces in the foveal or perifoveal regions of the retina and may complicate all forms of uveitis, including anterior uveitis.

Glaucoma may be secondary to steroid treatment or the result of ocular inflammation. Chorioretinal scarring at the macula can occur when an abnormal proliferation of choroidal blood vessels forms a choroidal neovascular membrane. These changes are similar to those observed in the “wet” form of age related macular degeneration.

In a retrospective study of a cohort of patients at a district general hospital, acute anterior uveitis had the lowest risk of visual loss, with 91% of patients retaining normal visual acuity (6/9 or better).⁶ Panuveitis carries the greatest risk of visual impairment.²

How is uveitis diagnosed?

The diagnosis of uveitis is confirmed with a slit lamp examination. A generalist can assess the patient’s visual acuity, look for circumcorneal injection, and examine the external eye with a direct ophthalmoscope (a +10 lens gives a magnified view). Urgent referral to a specialist is needed for further assessment, which includes measurement of intraocular pressure and a slit lamp examination to dilate the pupil (fig 2).

How is the cause of uveitis identified?

A detailed systemic history and a full physical examination is needed to establish whether uveitis is isolated or part of a multisystem disorder. Immune status should be considered as immunosuppressed patients are particularly at risk of infection related uveitis.

Systemic investigations should be directed at the likely cause of uveitis and are guided by the history, the pattern of ocular inflammation (box 2), systemic signs, and the local patient population. For example, for an adult patient presenting with a unilateral anterior uveitis, it would be important to ask about symptoms such as back pain, joint pains, stiffness, diarrhoea, and mouth ulcers that might link uveitis with a disease associated with HLA B27. An adult patient with a single attack of acute anterior uveitis and no signs or symptoms of systemic disease may not need any further investigations, and the value of routine HLA B27 testing in this setting is not clear.^{w16}

If infection related uveitis or malignancy is suspected, laboratory examination of an aqueous or vitreous sample using molecular techniques can be useful in making a diagnosis and guiding treatment.^{w17 w18}

How does ocular imaging help?

Ocular imaging is used to assess the site and severity of inflammation in the posterior segment of the eye and to monitor the response to treatment. Fundus fluorescein angiography is performed by giving an intravenous injection of dye and taking serial retinal images to show retinal vasculitis and retinal and choroidal disease (fig 3). Optical coherence tomography is a non-invasive technology that uses low coherence interferometry to produce high resolution, cross sectional images of the retina. It may be used to identify cystoid macular oedema and can provide an objective measure of retinal thickness (fig 4).^{w20}

What are the general principles of treating uveitis?

The management of uveitis is determined by whether uveitis is related to infection or is non-infective and by the likelihood of a threat to sight.⁷ Most patients with active uveitis and all those with acute anterior uveitis need treatment. Treatment is not needed for some forms of chronic

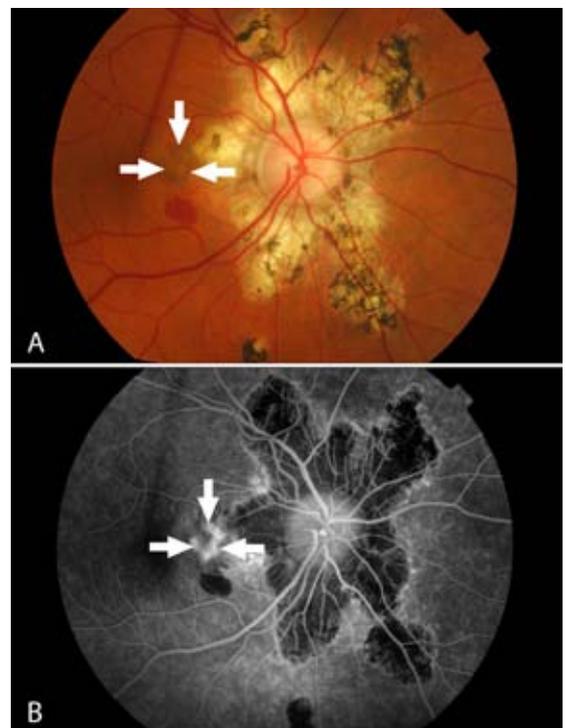


Fig 3 | Choroidal neovascular membrane in a uveitis entity known as serpiginous choroidopathy. The choroidal neovascular membrane can be seen as a grey lesion (arrows) with an adjacent haemorrhage on the retinal photograph (A) but is easier to see on the fluorescein angiogram (B), where it is a white colour because it fills with fluorescein dye. The oblique shadow is a marker that points to the fovea, and the close proximity of the choroidal neovascular membrane to the fovea makes this a sight threatening lesion. Atrophy of the retina and choroid around the optic disc (caused by previous inflammation) appears yellow and pigmented on the photograph but dark on the fluorescein angiogram because it is not perfused with dye

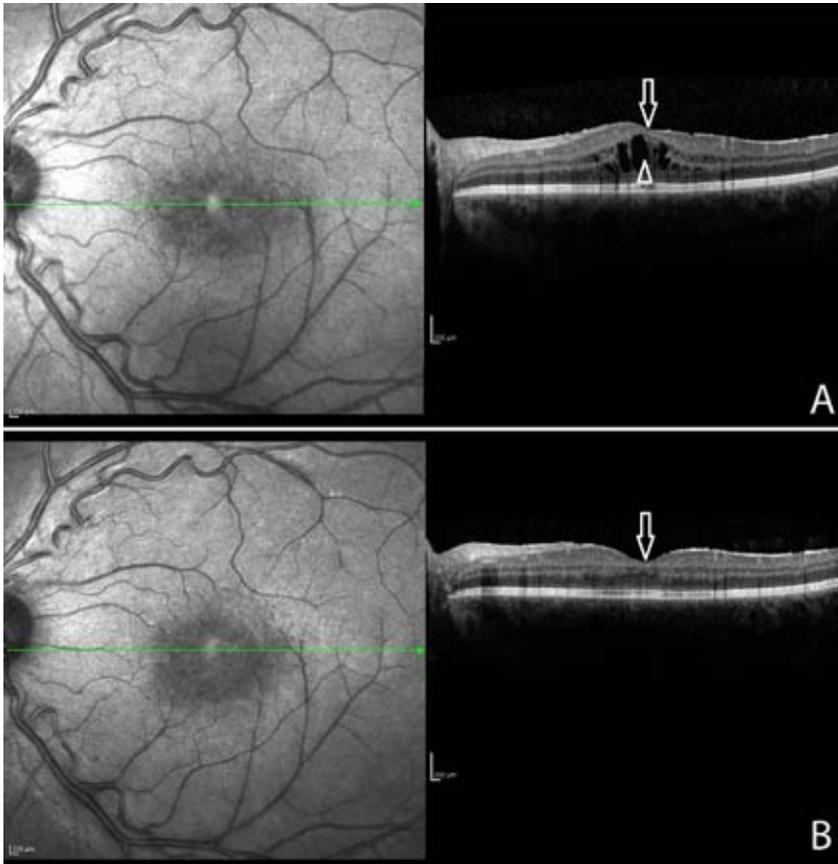


Fig 4 | Optical coherence tomography of the macula, centred on the fovea showing (A) cystoid macular oedema and (B) resolution after systemic treatment. The horizontal line on the left hand picture shows where the cross sectional image has been taken. The fovea (arrow) is normally thinner than the rest of the retina, but with cystoid macular oedema the normal architecture is lost and fluid filled cysts (arrow head tip) distort the retina

uveitis if the inflammation is not considered to be sight threatening. The aim of treatment is rapid resolution of ocular inflammation with restoration of vision. It is important to choose the drug and route of delivery to ensure penetration to the site of the ocular inflammation.

How is infection related uveitis treated?

In infection related uveitis the priority is to treat the underlying infection, with systemic treatment in the case of infections such as tuberculosis, syphilis, and Lyme dis-

ease and with a combination of systemic and intravitreal treatment in endogenous endophthalmitis. However, the immune response to the infection is thought to be partly responsible for the inflammation and for the resultant ocular damage and visual loss. It is for this reason that topical and systemic steroids are often used to suppress inflammation in patients with infection related uveitis⁷ and why in some instances uveitis persists after the infection has been treated. Topical steroids should be used with care in eyes with herpes simplex uveitis because of the risk of exacerbation of corneal epithelial disease.

Uveitis associated with toxoplasmosis

A Cochrane review of antibiotic treatment for ocular toxoplasmosis reported a lack of evidence for routine antibiotic treatment for acute toxoplasma retinochoroiditis⁸ but there were no trials evaluating modern antibiotic regimens.

Which treatments are used for non-infective acute anterior uveitis?

Topical steroids

A tapering course of topical steroids has been the standard treatment of acute anterior uveitis since the 1950s, although a systematic review found little evidence to support such drugs for anterior uveitis.⁹ A randomised controlled trial (RCT) found that the use of prednisolone acetate 1% eye drops is associated with resolution of symptoms and signs of acute anterior uveitis in 80-90% of patients at four weeks.¹⁰ Periocular steroid injections or systemic corticosteroids are used in severe cases of acute anterior uveitis and to treat cystoid macular oedema.

Dilation of the pupil

No evidence exists to support mydriatic use in uveitis, but standard practice is to dilate the pupil in the acute phase with a mydriatic agent such as cyclopentolate or atropine eye drops to try and break any posterior synechiae that have formed, reduce the formation of new posterior synechiae, and alleviate discomfort.

Which treatments are used for chronic non-infective uveitis?

Local treatments

Corticosteroids may be delivered topically as eye drops, locally as periocular or intravitreal injections, or as an intravitreal implant. Corticosteroids need to be used with care because of the associated complications, related to the dose and duration of treatment, which include raised intraocular pressure and formation of cataract.

Non-randomised interventional studies^{w40 w41} and retrospective case series^{w42} found that intravitreal corticosteroid injections were associated with a significant short term improvement in visual acuity, but the temporary treatment effect limits their usefulness for treating chronic uveitis.¹¹

A randomised prospective study found that a fluocinolone acetonide corticosteroid implant surgically implanted into the vitreous cavity achieved better control of ocular inflammation than systemic steroids and non-biological immunosuppressive agents, but of the

A PATIENT'S PERSPECTIVE

"I am a 50 year old woman. My uveitis started 22 years ago, when I woke up with a painful red eye. The doctor said it was an infection but the eye got worse and eventually I was referred to the hospital, where they told me I had uveitis. They gave me injections of steroid into the eye, which calmed things down, but it flared up again . . . I was given more injections of steroid but then I developed a cataract. After the cataract surgery I went blind in that eye.

"A few years later I got uveitis in the other eye. I was referred to Aberdeen and started on ciclosporin, which worked for many years but then started to interfere with my kidneys, and I had to be changed to mycophenolate. At the millennium I developed optic neuritis and multiple sclerosis and was having difficulty with my work as a primary school teacher. I was given a scribe and smaller classes—thank goodness for the Disability Discrimination Act.

"My vision has been getting worse recently, but I had been putting off cataract surgery as I was terrified of losing the vision in my only eye. I had the operation yesterday and today I can see some letters on the [Snellen] chart again. If my vision stays like this I can manage."

Note: The patient's visual acuity had improved from "count fingers" (worse than 6/60) to 6/18

TOPICS FOR FURTHER RESEARCH

- Clinical efficacy, safety, and cost effectiveness of intravitreal treatments and biological agents for uveitis
- The targeted approach—identifying and precisely targeting the immune mediators responsible for different forms of uveitis
- Measures of efficacy for clinical trials—single or composite end points?
- Use of non-invasive ocular imaging to provide objective and reproducible measures of disease activity
- Improved diagnostic methods for detecting infectious uveitis

ADDITIONAL EDUCATIONAL RESOURCES

For health professionals

- Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol* 2000;130:492-513.
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For patients

- Uveitis Information Group (www.uveitis.net)—Patient led organisation that has links with ophthalmologists. The group runs an informative website and produces a magazine (*Uveitis*) for patients and clinicians
- Birdshot Uveitis Society (www.birdshot.org.uk)—Affiliated to the Uveitis Information Group, this is a support group for patients with birdshot chorioretinopathy
- Behçet's Syndrome Society (www.behcets.org.uk)—Provides support and information on all aspects of Behçet's syndrome, including uveitis
- Royal National Institute of Blind People (www.rnib.org.uk)—Works to enable people with sight loss to live their lives independently

eyes with an implant that started the trial with a natural lens, most (88%) went on to have cataract surgery and 21% required glaucoma surgery.¹²

Bevacizumab and ranibizumab are vascular endothelial growth factor inhibitors that have been used as intravitreal injections for uveitis after their success in treating choroidal neovascular membranes associated with age related macular degeneration. Neither drug is licensed for use in uveitis, and only ranibizumab is licensed for treating age related macular degeneration. A clinically significant improvement in visual acuity was reported in a large retrospective series of patients with inflammatory choroidal neovascular membranes treated with bevacizumab,¹³ The treatment effects of intravitreal drugs are transient, necessitating repeated injections. Each injection carries a small but additive risk of visual loss from complications such as endophthalmitis, cataract, and retinal detachment.

Systemic steroids and immunosuppression

International guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders were published in 2000.¹⁴ Currently, no licensed immunosuppressive treatments are available for uveitis.

The guidelines recommend corticosteroids as the first line systemic treatment for patients with sight threatening uveitis. Systemic corticosteroids are usually started at a high dose and then tapered. Systemic immunosuppression may be started for patients who have poorly controlled ocular inflammation with systemic steroids or for patients in whom ocular inflammation has recurred on reducing the steroid dose. Immunosuppressive treatment

is begun early in the treatment of certain diseases—for example, posterior disease or panuveitis associated with Behçet's syndrome, in which visual outcomes have been shown to be poor with corticosteroids alone.¹⁴

Small RCTs of azathioprine, ciclosporin, and tacrolimus and large retrospective series of patients taking mycophenolate mofetil and methotrexate have reported benefit from these drugs in the control of ocular inflammation and the preservation or restoration of sight in uveitis.^{15-19 w45}

Biological agents

Biological agents have recently been introduced for patients who have not responded to treatment with systemic steroids and one or more of the conventional immunosuppressive agents. However, the findings of a retrospective study²⁰ support a growing opinion among experts²¹ that early use of biologics in patients with severe, sight threatening ocular inflammation may prevent sight loss more effectively than when these agents are used as a last resort.

Infliximab and adalimumab are tumour necrosis factor α inhibitors that have been shown in small, prospective, non-randomised studies to control ocular inflammation in adults and children with uveitis that is refractory to other immunosuppressive agents.^{22 23} Interferon α has been used with notable success in Behçet's syndrome, with control of ocular inflammation achieved in 92% of patients in one non-randomised trial,²⁴ and has been shown to be effective in uveitic cystoid macular oedema in two non-randomised trials.^{25 26}

What are the risks of immunosuppressive treatment for uveitis?

Data on the risk of infection with long term immunosuppression for uveitis are limited, but reported trials and case series seem to show that the risk of serious infections is low.^{15-19 22-26 w45 w55-w57} Most commonly used immunosuppressive drugs did not increase overall mortality or cancer related mortality in a large retrospective cohort study of patients with ocular inflammatory disease.²⁷ Whether tumour necrosis factor inhibitors increase mortality or carry a risk of neoplasia in patients with ocular inflammation is not clear.²⁷

Can surgery can help?

Ocular surgery may be indicated (a) to obtain ocular samples for diagnostic purposes, (b) to allow visual rehabilitation through cataract or vitrectomy surgery, and (c) for preservation of vision in uveitic glaucoma.

Which patients should be screened for uveitis?

Children with juvenile idiopathic arthritis should be screened for uveitis with regular slit lamp examinations. Best practice guidelines for screening were issued jointly by the Royal College of Ophthalmologists and the British Society for Paediatric and Adolescent Rheumatology in 2006.²⁸

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Competing interests: All authors have completed the Unified Competing Interest form at http://www.icmje.org/doi_disclosure.pdf (available on request from the corresponding author) and declare that (1) the authors have no financial support for the submitted work; (2) JVF does consultancy for Abbott and is due to participate in a research trial involving adalimumab; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) the authors have no non-financial interests that may be relevant to the submitted work.

Provenance and peer review: Not commissioned; externally peer reviewed.

Patient consent obtained.

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ANSWERS TO ENDGAMES, p 839. For long answers go to the Education channel on bmj.com

CASE REPORT Abdominal pain and diarrhoea in a teenager

- Differential diagnoses to be considered are inflammatory bowel disease, coeliac disease, Meckel's diverticulum, infection, solitary rectal ulcer, allergic colitis, intussusception, and constipation with overflow and concurrent anal fissure. The most likely diagnosis is inflammatory bowel disease and, in this case, Crohn's disease.
- Growth failure, lethargy, pubertal delay, arthropathy, psychiatric disturbances, and nausea with or without vomiting are all found in inflammatory bowel disease. Extraintestinal manifestations such as erythema nodosum and pyoderma gangrenosum are found in both ulcerative colitis and Crohn's disease. Lip swelling, mouth ulcers, and orofacial granulomatosis, along with perianal disease (skin tags, fissures, fistulas, and abscesses), are also found in Crohn's disease.
- Children presenting with these symptoms should have a full blood count; tests for erythrocyte sedimentation rate, serum urea, serum creatinine, and serum albumin; and a coeliac screen. All children suspected of having inflammatory bowel disease should undergo upper and lower gastrointestinal endoscopy with biopsies taken at all levels irrespective of the presence or absence of symptoms in the upper gastrointestinal tract. Imaging of the small bowel should also be considered in all children with Crohn's disease and in those in whom a diagnosis of ulcerative colitis is uncertain. Radiography with small bowel follow through is the most commonly used imaging technique; however, white cell scanning or gadolinium enhanced magnetic resonance imaging are other suitable methods.
- Exclusive enteral nutrition or steroids should be considered to induce remission. Both have equal efficacy, but enteral nutrition is now the standard practice in paediatrics because it offers nutritional support as well as inducing remission. Using exclusive enteral nutrition also avoids the side effects that are associated with the use of high dose steroids.
- Once the patient's clinical condition has improved, immunosuppressant therapy with an agent such as azathioprine or mercaptopurine should be discussed with the child and their family.

STATISTICAL QUESTION

Number needed to treat

Answers *b* and *c* are true, whereas *a* and *d* are false.

ON EXAMINATION QUIZ

Tourniquets

Answers B and C are correct.

ANATOMY QUIZ

Coronal computed tomography of the sinuses

- A Right maxillary infundibulum
- B Right middle turbinate
- C Right maxillary antrum
- D Crista galli
- E Left inferior turbinate