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The Role of Primary Care Providers for Uveitis

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A B S T R A C T

Uveitis, a treatable sight-threatening condition, may often be misdiagnosed and treated as pink eye, a common ophthalmic condition encountered in the primary care setting. Although more than 50% of cases of uveitis are idiopathic, a variety of underlying medical conditions, such as genetic, traumatic, systemic immune-mediated conditions, or infectious mechanisms can trigger uveitis. An accurate and prompt diagnosis is critical for initiating vision-saving treatment. Because a high percentage of uveitis was reported in the primary care setting, the role of primary care providers should focus on identifying the condition, initiating first-line therapy, and promptly referring to an ophthalmologist.
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In the United States, pink eye accounts for 1% of primary care office visits, and 70% of patients with pink eye are treated at primary care and urgent care settings.[1] Viral infection is the most common etiology for pink eye.[2] However, uveitis, a treatable, vision-threatening condition, may often be misdiagnosed and treated as pink eye.[3] Ninety percent of all cases of uveitis were reported in the primary care settings.[4,5] Therefore, it is critical for primary care providers to be able to accurately and promptly diagnose uveitis to avoid vision-threatening sequelae.

Causes

Uveitis is an inflammatory condition affecting the uveal tract (pigmented portion) of the eye, which includes the iris, ciliary body, and choroid.[3,6] Although it primarily affects the uveal tract (Figure 1), the inflammation of uveitis may involve adjacent structures such as the retina, optic nerve, and vitreous humor. Genetic, traumatic, systemic immune-mediated causes or infectious mechanisms may trigger uveitis.[3,7] According to Tsirouki et al,[8] human leukocyte antigen B27 (HLA-B27)-associated anterior uveitis (Figure 2) is the most common noninfectious uveitis (NIU). Some HLA-B27-related diseases include ankylosing spondylitis, inflammatory bowel disease, psoriatic arthritis, and Reiter's syndrome. Other systemic diseases that may trigger uveitis include sarcoidosis, tuberculosis, Lyme diseases, syphilis, and autoimmune diseases, such as juvenile rheumatoid arthritis.[3,9] Gritz et al[10] reported cytomegalovirus (CMV), varicella zoster virus (VZV), herpes simplex virus (HSV), and toxoplasmosis as common infectious agents responsible for infectious uveitis. However, up to 60% of cases of uveitis have been reported to be idiopathic.[8,10] Consequently, the appropriate patient workup for possible etiologies may often yield no confirmatory results.

Types and Prevalence of Uveitis

The most common type of uveitis is acute anterior uveitis (AAU).[3,4,8,11] AAU involves mainly the iris and/or ciliary body. Young and middle-aged patients are more frequently affected. Intermediate uveitis involves the pars plana and vitreous humor. This type of uveitis commonly affects young adults. Posterior uveitis is the least common type of uveitis, and it involves the vitreous humor and chorioretinal layers. Posterior uveitis is the most responsible for profound vision loss if left untreated. Panuveitis is a term used when inflammation is seen in all 3 areas.

Several epidemiology studies show the variability in prevalence and incidence of different types of uveitis. Thorne et al[12] conducted a claim-based analysis using data from 4 million privately insured individuals. The purpose of the analysis was to estimate the prevalence of NIU in 2012. According to their analysis, the prevalence of NIU was 121 per 100,000 adults and 29 per 100,000 children. Anterior NIU accounted for 81% (3,904 cases) in adults and 75% (207 cases) in pediatrics. Another claim-based analysis was conducted by Zhang et al.[13] They used administrative insurance claims from 21.5 million privately insured individuals between 2007 and 2015 to estimate the prevalence of infectious uveitis and scleritis. The mean annual incidence and prevalence of infectious uveitis/scleritis were 18.9 and 60.6 per 100,000 persons, respectively. This accounts for approximately 14% of uveitis/scleritis cases. Tsirouki et al[8] conducted an extensive literature review with a focus on the epidemiology of uveitis. Their review included studies from other countries. The result showed that uveitis most frequently affected adults between the ages of 20 to 50. HLA-B27 associated uveitis was more commonly found in young adults.

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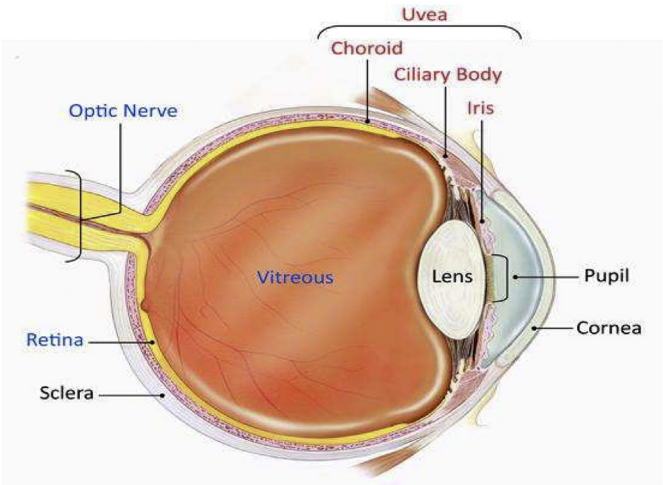

Figure 1. Uveal tract. Uvea comprises the choroid, ciliary body, and iris. Courtesy of the National Eye Institute, National Institutes of Health. https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/uveitis

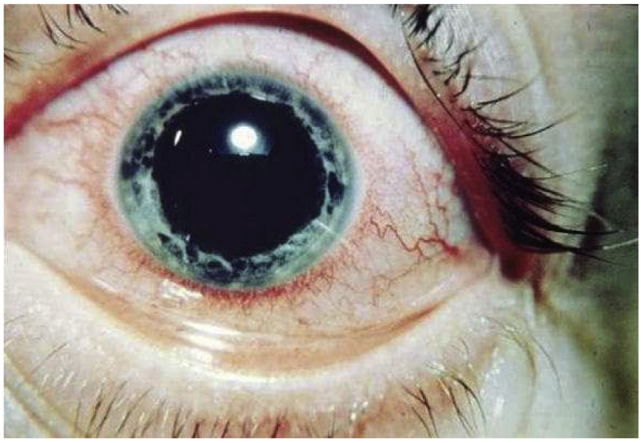

Figure 2. Acute anterior uveitis. Acute anterior uveitis in ankylosing spondylitis. Redness around the cornea (ciliary flush) is a typical sign of acute uveitis. Note irregular-shaped pupil. Courtesy of Paul Dieppe, BSc, FRCP, FFPHM, from Nguyen HD, HLA-B27 syndromes. Medscape; April 9, 2021. https://emedicine.medscape.com/article/1201027-overview

Clinical Manifestations

Different types of uveitis present with slightly different symptomology (Table 1).[3,7] The most common symptoms of AAU include pain, redness (hyperemia), photophobia, blurred vision, and epiphora (watery eyes). Pain occurs over several hours to days. Hyperemia is usually noted on the corneal limbus. This is known as limbal flush, or ciliary flush. The main symptoms of chronic anterior uveitis are blurred vision and mild redness. Pain and photophobia may occur, but they are usually mild. Chief complaints of patients with intermediate or posterior uveitis include blurred vision and nonspecific visual changes such as floaters and/or decreased visual acuity in the absence of symptoms of AAU. Any of the preceding symptoms can be associated with panuveitis.[3,14] Common physical findings of uveitis include miosis or an irregular-shaped pupil. Ciliary flush, a deep conjunctival injection (Figure 2), is commonly seen in anterior uveitis. It gets more intense near the limbus (a violaceous ring around the cornea) and is easily observed in natural daylight.[7] However, examination of ocular adnexa (eyelids, lashes, and lacrimal ducts) will primarily be within the normal range. Extraocular movements are usually normal. In addition to any ophthalmologic manifestations, patients with uveitis-triggering underlying conditions may present with symptoms related to systemic, immune-mediated diseases, such as chronic back pain, enthesitis, joint swelling, or arthritis.

Complications

Uveitis may cause various complications. Complications include but are not limited to deposition of calcium in the epithelium of the cornea (band keratopathy), adhesion of the iris to the lens (posterior synechiae), cataracts, intraocular hypertension, glaucoma, and fluid accumulation in the area of the central retina (cystoid macular edema).[3] In addition, optic nerve atrophy and permanent vision loss may result from an acute rise in intraocular pressure, scar tissue, obstruction, or steroid response. There are no large-scale epidemiology studies about the impact of uveitis on vision loss. However, several smaller and retrospective studies reported data about vision loss by uveitis. The Northern California Epidemiology of Uveitis Study[10] is the community-based, cross-sectional retrospective cohort study in the United States with 844 cases of uveitis. The study reported that 19.1% of their patients (n = 116) experienced various types of vision loss, including long-term (>3 months) and transient legal blindness. Their multivariate analysis showed that the course of the disease, whether acute, recurrent, or chronic, was the statistically significant predictor of vision loss as well as disease location ($p < 0.001$); 29.9% of patients with chronic uveitis experienced a long-term vision loss, 5.7% and 10.8%, respectively, for acute and recurrent uveitis patients. Anterior uveitis had the lowest odds of experiencing vision loss, and 29.5% of their sample developed 1 or more complications. Chronic uveitis and the history of prior onset of glaucoma were statistically associated with uveitic glaucoma ($p < 0.001$). Age was associated with an increased rate of complications. Tomkins-Netzer et al[15] conducted a prospective study to evaluate the long-term outcomes of vision loss in patients with uveitis. They recruited 1076 patients followed up for an average of 8 years. Their study reported that 158 out of 1,799 eyes from 1,076 patients developed permanent and moderate vision loss, and 164 eyes developed permanent and severe vision loss. Chronic cystoid macular edema and macular scarring were the most common causes of vision loss. Other studies in India and Finland[16,17] with small samples of 50 and 176 cases reported between 22% and 37% of vision loss, respectively. The study by Fanlo et al[18] involving 500 adult patients in Spain reported a 35% complication rate, with glaucoma being the most frequent complication. They also reported that older age increased the risk of vision loss.

Diagnostic Evaluation and Referral

Diagnosing uveitis requires an anterior segment examination via slit-lamp microscopy and a dilated fundus examination (DFE).[3,14] White blood cell clumps (keratic precipitates; Figure 3) on the inner corneal surface seen during the slit-lamp examination is pathognomic for anterior uveitis. Intermediate and posterior uveitis is usually diagnosed by direct visualization of the middle and posterior parts of the eyes. Active chorioretinal inflammation and/or leukocytes are the key findings in posterior uveitis. Exudates or "snowbanks" between the retina and the ciliary body, the area known as the pars plana, are typical findings of intermediate uveitis. Diagnostic key findings are listed in Table 2. However, a slip-lamp examination and DFE may not be available in most primary care settings due to a lack of ophthalmic training and experience. Therefore, detailed medical history and review of systems (ROS) are

Table 1
Clinical Manifestations of Different Types of Uveitis

	Symptoms	Signs
Anterior	Acute • Gradual pain over hours or days • Redness (hyperemia) • Photophobia • Epiphora (watery eyes) • Decreased vision Chronic: • Blurred vision • Mild redness	Physical examination • Normal lids, lashes, and lacrimal ducts • Extraocular movements are normal. • Corneal limbal flush (360 perilimbal injection increases near the limbus) • Direct and consensual Photophobia • Pupillary miosis
Intermediate and posterior	• Painless • Nonspecific visual changes: floaters and/or reduced visual acuity • Redness not prominent	Physical examination • Normal lids, lashes, and lacrimal ducts • Extraocular movements are normal. • Redness is not a prominent feature. • No photophobia • Pupillary miosis

imperative. Inquiry regarding symptoms associated with systemic, immune-mediated diseases, such as the history of back pain, enthesitis, joint swelling, or arthritis, is also necessary.[19,20]

There is no standard diagnostic workup for uveitis because it is associated with many medical conditions.[3,20,21] Providers may consider ordering diagnostic tests to rule out the suspected causes when clinical features suggest underlying etiologies. Complete blood cell counts, erythrocyte sedimentation rate, antinuclear antibody, rapid plasma reagin, venereal disease research laboratory, purified protein derivative test, Lyme titer, HLA-B27, urinalysis, or HIV test are some examples of laboratory studies to consider.[3,6,20,22] However, if uveitis is suspected after thorough history-taking and physical examination, prompt referral to an ophthalmologist is necessary for a slit-lamp examination and DFE to confirm the diagnosis. The earlier the diagnosis by an ophthalmologist, the better the prognosis. Early intervention leads to a better chance of preserving vision.[3,14] Primary care providers should remember the mnemonic "RSVP" to identify those patients in need of a referral to an ophthalmologist (persistent Redness, Sensitivity to light, usually with anterior uveitis, Visual change, Pain; Table 3).[3]

Differential Diagnoses

Other medical conditions may present with similar symptoms of uveitis. A differential diagnosis of eye conditions that may mimic uveitis follows.[3,21-23] Intraocular lymphoma is a red flag condition for uveitis, and it occurs insidiously, usually in both eyes. Often vitritis, chorioretinal infiltrates, and sometimes anterior chamber inflammation occur with intraocular lymphoma. Inflammation from this disease is refractory to the treatment with corticosteroid. When a patient presents with a new onset of bilateral ophthalmic inflammation after age 45 or with focal neurological deficit or when corticosteroid treatment is ineffective, workup to rule out intraocular lymphoma should be initiated in this situation. Intraocular lymphoma is one of the masquerade syndromes. This term is used to describe malignant or nonmalignant ocular disorders that share the common characteristic of intraocular inflammation that is not from uveitis.[6,23]

- Intraocular lymphoma
- Acute angle-closure glaucoma
- Acute conjunctivitis (pink eye)
- Corneal ulcer and ulcerative keratitis
- Corneal abrasion
- HSV keratitis
- Intraocular foreign body
- Scleritis
- Ultraviolet keratitis

Treatment and the Role of Primary Care Providers

The main goals of care in primary care settings include accurate and prompt diagnosis and referral to an ophthalmologist.[6,21,24-26] Providing proper pain relief also should be considered as one of the main goals. Uveitis treatments include cycloplegics, antimicrobials, topical or systemic corticosteroid, and immunomodulatory drugs. Treatments for uveitis should be initiated within 24 hours. Patients with possible uveitis should be examined by an ophthalmologist within 24 hours to minimize sequelae and recurrence.

Topical cycloplegics (anticholinergics) are frequently used to relieve pain and photophobia. This class of medication reduces pain and photophobia by relaxing the ciliary spasms of the pupil.[6,26] Cyclopentolate ophthalmic (Cyclogyl) 0.5%, 1%, and 2% solutions and homatropine ophthalmic 5% solution are the common agents. Duration of cyclopentolate may not be long enough for severe anterior uveitis. Therefore, homatropine is a preferred choice of medication for uveitis. Cycloplegia by homatropine lasts 10 to 48 hours, and mydriasis lasts 6 hours to 4 days. The usual dose of homatropine is 1 to 2 drops every 3 to 4 hours. The usual dose of cyclopentolate is 1 drop of 1% solution 3 times daily. Despite the fact that the use of cycloplegic drops is not approved by the US Food and Drug Administration for the management of pain and

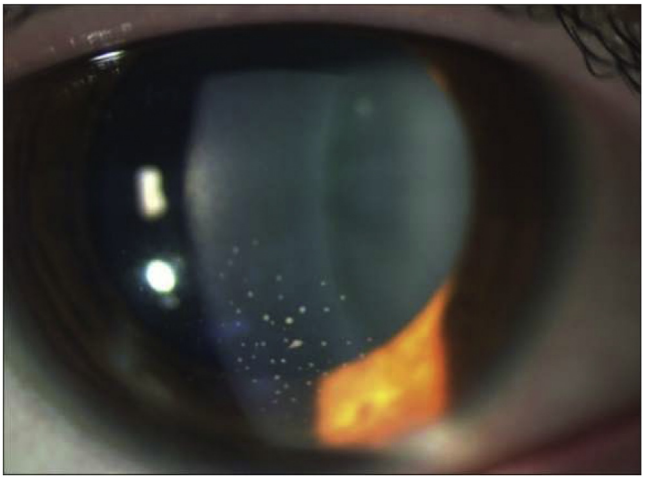

Figure 3. Keratic precipitates. As seen in this slit lamp examination, clumps of white blood cells are called keratic precipitates. Tekin K, Erol YO, Kurtulan O, Baydar DE. A case of adult-onset tubulointerstitial nephritis and uveitis syndrome presenting with granulomatous panuveitis. *Taiwan J Ophthalmol.* 2020;10(1):66-70. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7158930/

Table 2
Diagnostic Key Findings of Uveitis

Types of Uveitis	Diagnostic Findings
Anterior	Slit-lamp examination: • Keratic precipitates: white blood cell clumps on the inner corneal surface • Cells and flare (a haze) in the anterior chamber and posterior synechiae due to the large collection of inflammatory cells in the vitreous • Hypopyon: white blood cells layer in the anterior chamber with severe anterior uveitis
Intermediate and posterior	A dilated fundus examination: • Active chorioretinal inflammation and/or leukocytes • Exudates or "snowbanks" between the retina and the ciliary body

photophobia associated with uveitis, the use of cycloplegics for this indication is the community standard of care among ophthalmologists (Table 4).

Generally, antibiotics are not indicated for uveitis.[6] However, antibiotics may sometimes be employed for the management of possible uveitis of unknown etiology. CMV, VZV, and HSV are the most common infectious agents responsible for uveitis. Oral acyclovir, valacyclovir, and famciclovir are the mainstay of treatment for HSV- and VZV-induced infections. Valganciclovir is used for CMV-induced infections.[26-28]

Topical corticosteroid is the first choice of medication for noninfectious anterior uveitis. 1 to 2 drops of prednisolone acetate ophthalmic 1% solution or suspension can be prescribed 2 to 4 times daily.[26,28] Pred Forte (prednisolone acetate suspension 1%) and Pred Mild (prednisolone acetate suspension 0.1%) are available brand name products in the United States. A more potent topical corticosteroid is Durezol (difluprednate ophthalmic suspension 0.05%). This medication is known to have a better vitreous humor penetration and delivery to the posterior area of the lens. More potent corticosteroids have a greater risk of steroid-related complications such as cataracts and glaucoma. If signs and symptoms fail to improve after 2 days, a reevaluation of patients should follow.

Patients resistant to initial treatment with ongoing inflammation may be treated with systemic corticosteroid or other immunosuppressive agents such as calcineurin antagonist or tumor necrosis factor inhibitors. Although the dose and duration of systemic corticosteroid should differ based on the severity of uveitis and underlying diseases, the equivalent of 40 to 60 mg of prednisone per day is a usual initial dose of systemic corticosteroid. Using the lowest dose possible to reduce inflammation efficiently should be the goal of the providers.[22,26,28] In addition, 2 sustained-release corticosteroid vitreous implants, fluocinolone acetonide (Retisert, Yutiq) and dexamethasone (Ozurdex), are available.[22] They provide 30 to 36 months of continuous treatment and could reduce risks associated with the use of oral corticosteroids. Immunosuppressive agents include methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, infliximab, etanercept, and adalimumab.[6,21] However, these treatment options should be reserved for severe and chronic uveitis and initiated by an ophthalmologist or rheumatologist.[24]

Table 3
Mnemonic for Referral

Letter	Description
R	Persistent redness
S	Sensitivity to light, usually with anterior uveitis
V	Visual change
P	Pain, prominent in acute anterior uveitis

Table 4
Medications

Classes (Ophthalmic)	Drug Names	Usual Dosage
Topical cycloplegic	Cyclopentolate 0.5%, 1%, 2%	1% 1 gtt TID (off-label)
	Homatropine 5%	1–2 gtt every 3–4 hours
Topical corticosteroid	Pred Forte 1 %	1–2 gtt BID to QID
	Pred Mild 0.12 %	1–2 gtt BID to QID
	Difluprednate 0.05%	1 gtt QID

BID = twice daily; gtt = drops; QID = 4 times daily; TID = 3 times daily.

Follow-Up Care and Patient Education

Anticipatory guidance upon referring a patient to an ophthalmologist is critical. The potential adverse effects of medications should be discussed thoroughly. Patients need to understand the importance of medication adherence and urgent follow-up with the ophthalmologist regardless of symptomatic improvement. Patients with AAU may need to be monitored every 1–7 days by the ophthalmologist. Once uveitis stabilizes, primary care providers may comanage the patients every 1–6 months. UpToDate offers 2 levels of patient education materials free of charge: "The Basics" and "Beyond the Basics."[3] The first is written at the 5th- to 6th-grade reading level and the second at the 10th- to 12th-grade reading level. The American Academy of Ophthalmology has a 9.5-grade level, 2-page short patient education brochure about uveitis that primary care providers may use for patients with uveitis. This education brochure is available only through purchase at their website.

Conclusion

Uveitis is a vision-threatening condition that masquerades as pink eye. To the casual primary care provider, the condition can easily be overlooked and misdiagnosed as pink eye. Primary care providers should have greater familiarity with uveitis and better knowledge of how to differentiate uveitis from pink eye. The consequences of making a misdiagnosis can lead to grave visual morbidity. Prompt identification, treatment, and referral can result in prevention of blindness. When encountering any form of pink eye in the primary care setting, the provider should always be reminded of RSVP (Table 3). These findings should lower the threshold for the diagnosis of uveitis.

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