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A Stepwise Approach to Diagnosing and Managing Anterior Uveitis

By Jim S. Xie, BHSc, and Alexander J. Kaplan, MD, FRCSC

Uveitis is the cause of up to 15% of blindness in developed countries as well as serious morbidity that reduces patients' productivity and quality of life. Although early identification of uveitis is essential to minimizing the long-term effects, diagnosis can be complicated by its variable presentation. This issue of *Ophthalmology Rounds* reviews the epidemiology, clinical features, diagnosis, and management of anterior uveitis. Particular emphasis is placed on developing a stepwise strategy for approaching these cases. We outline a standardized diagnostic algorithm that aims to optimize clinical yield while minimizing unnecessary patient harm and resource expenditure.

Introduction

Uveitis describes inflammation of the uveal tract (i.e., iris, ciliary body, and choroid) that may extend to other ocular structures, including the sclera, retina, retinal blood vessels, and optic nerve. The Standardization of Uveitis Nomenclature Working Group classifies uveitis anatomically into anterior uveitis (iritis, iridocyclitis, and anterior cyclitis); intermediate uveitis (pars planitis, posterior cyclitis, and hyalitis); posterior uveitis (choroiditis, chorioretinitis, retinochoroiditis, retinitis, and neuroretinitis); and panuveitis (anterior, intermediate, and posterior uveitis in combination).[1] Although inflammation of the posterior segment is more likely to be sight-threatening, poorly treated anterior uveitis may also result in permanent and debilitating vision loss.

The visual morbidity from uveitis imposes a significant burden on a patient's livelihood and quality of life,[2,3] as well as on economic productivity and healthcare resource use.[4,5] Early detection of uveitis and treatment targeted at the underlying etiology are crucial to reducing visual morbidity;[6] however, uveitis presents a diagnostic challenge due to its wide array of etiologies and clinical manifestations. Causes of uveitis can be broadly categorized as infectious, noninfectious, or masquerade. Table 1 presents a comprehensive differential diagnosis of anterior uveitis.[7-10]

Epidemiology

Uveitis is a leading cause of blindness worldwide and accounts for 10%-15% of blindness in developed countries.[11-13] Estimates of uveitis reported in population- and referral centre-based studies vary widely due to heterogeneity in participant selection, disease definition, demographics, and geographical region.[14-16] Population-based studies have estimated the prevalence of uveitis to range between 2 to 730 per 100 000 persons.[13,17]

Uveitis can affect any age but is most common between the third and sixth decades of life.[18] The prevalence of noninfectious uveitis has been shown to increase with age,[19,20] which may be related to increased incidence of ocular surgery and autoimmune disorders.[21,22] Females may have an increased risk of developing noninfectious uveitis due to hormone- and immune-mediated susceptibility.[23] Sex-based differences in uveitis incidence are highest in older age groups.[24] Ethnic and genetic factors may also predispose individuals to uveitis; for example, Vogt-Koyanagi-Harada disease, which is characterized by panuveitis with serous retinal detachments, more commonly affects individuals with higher skin pigmentation (e.g., Native American, Hispanic).[25,26] A history of smoking and vitamin D deficiency have been associated with increased risk of anterior uveitis.[27-33] Pregnancy seems to have a protective effect on uveitis flares in the second and third trimesters,[34] but pre-eclampsia and eclampsia appear to increase risk.[35]

The anterior segment is the most frequently affected anatomical location in uveitis, followed by posterior uveitis, panuveitis, and intermediate uveitis.[36-40] Based on data from referral centre-based studies around the world, the most common etiologies of uveitis are idiopathic (25%–77%),[36,41,42] infectious (9%–33%),[36,41] and noninfectious but related to a systemic autoimmune disorder (11%–33%).[43,44]

Clinical features

The onset, course, symptomatology, ocular signs, and response of anterior uveitis to treatment are helpful to uncover systemic disease and narrow the differential diagnosis. A dilated fundus examination must be performed in every patient to rule out inflammatory involvement of the posterior segment.

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Ophthalmology & Vision Sciences
UNIVERSITY OF TORONTO

Department of Ophthalmology and Vision Sciences, Faculty of Medicine University of Toronto,
60 Murray St.
Suite 1-003
Toronto, ON M5G 1X5

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Table 1. Limited differential diagnosis of anterior uveitis[7–10]

Infectious		
Viral		**Bacterial**
Herpes family – HSV, VZV, CMV, EBV COVID-19 Rubella HTLV-1	West Nile fever Chikungunya Parvovirus Ebola Zika	Syphilis Tuberculosis Post-streptococcal infection
Noninfectious		
Systemic autoimmune disorders	**Ocular entities**	**Traumatic syndromes**
Spondyloarthropathies HLA-B27-associated conditions[a] JIA Sarcoidosis Chronic VKH TINU	HLA-B27 without systemic manifestations Lens-induced uveitis FHI PSS Sympathetic ophthalmia	Post-traumatic Postsurgical Intraocular foreign body UGH TASS
Medication-induced	**Masquerade syndromes**	
Cidofovir Rifabutin Fluoroquinolone Bisphosphonate Sulfonamide Etanercept	Hematological neoplasm – Lymphoma, leukemia, multiple myeloma Metastasis Pigment dispersion syndrome	

[a]Includes ankylosing spondylitis, reactive arthritis, Behçet disease, inflammatory bowel disease, and psoriatic arthritis.
CMV, cytomegalovirus; EBV, Epstein-Barr virus; FHI, Fuchs heterochromic uveitis; HLA-B27, human leukocyte antigen B27; HSV, herpes simplex virus; HTLV-1, human T-lymphotropic virus type 1; JIA, juvenile idiopathic arthritis; PSS, Posner-Schlossman syndrome; TASS, toxic anterior segment syndrome; TINU, tubulointerstitial nephritis and uveitis; UGH, uveitis-glaucoma-hyphema syndrome; VKH, Vogt-Koyanagi-Harada disease; VZV, varicella zoster virus

If the fundus is not visible at the initial consultation, B-scan ultrasonography should be performed to assess for the presence of vitritis, retinal detachment, and choroidal or scleral thickening. Frequent ocular examinations while on topical steroids are often necessary. Posterior segment involvement necessitates a referral to a retina/uveitis specialist.[45]

Symptomatic patients commonly present with pain, redness, photophobia, and blurry vision. Redness and pain are usually absent in intermediate and posterior uveitis.[46] Asymptomatic anterior uveitis should raise suspicion of chronic etiologies such as Fuchs heterochromic iridocyclitis (FHI) and juvenile idiopathic arthritis (JIA). Bilateral anterior uveitis can be associated with systemic autoimmune conditions such as sarcoidosis and Behçet disease (BD). Unilateral involvement is characteristic of acute idiopathic etiologies, FHI, and viral associated anterior uveitis.[47] Alternating, unilateral episodes of anterior uveitis is suggestive of a human leukocyte antigen (HLA)-B27-related cause.

Intraocular pressure (IOP) is typically decreased in both acute and chronic anterior uveitis due to ciliary body insult. Rarely, IOP may be elevated from open- and closed-angle mechanisms. Intraocular infections (e.g., herpes simplex virus, varicella zoster virus, cytomegalovirus, and Epstein-Barr virus) and FHI may result in elevated IOP in unilateral cases, and sarcoidosis and tuberculosis (TB) in bilateral cases with extensive posterior synechiae.[8] Raised IOP should also prompt consideration of a medication-related steroid response, lens-induced uveitis, or a pseudophakic uveitis-glaucoma-hyphema syndrome.

Nongranulomatous forms of anterior uveitis usually involve dust-like keratic precipitates (KPs) and fibrin in the anterior chamber (AC), which may form membranes that occlude the pupil to varying degrees. Anterior uveitis associated with HLA-B27 positivity and BD is always nongranulomatous. Similarly, acute, idiopathic anterior uveitis tends to involve nongranulomatous pathology. KPs may also be stellate and diffusely arranged across the corneal endothelium (e.g., FHI); moderately sized, ground glass, or dendritiform and situated centrally or paracentrally (e.g., herpes virus); or large KPs, resembling mutton fat, and organized in an inferior triangular distribution (e.g., sarcoidosis and TB).[47] Additional corneal signs that suggest herpetic anterior uveitis include keratouveitis and corneal hypoesthesia.

Examine the iris before and after mydriasis. Sectoral iris atrophy is associated with herpetic infection and diffuse iris atrophy is associated with chronic longstanding uveitis, FHI, and moxifloxacin-induced anterior uveitis.[47] Iris heterochromia with loss of iris crypts is pathognomonic of FHI. The presence of iris nodules, either at the pupillary margin (i.e., Koeppe nodules) or within the iris stroma (i.e., Busacca nodules), is indicative of granulomatous inflammation. Identification of posterior synechiae post-mydriasis rules out FHI and viral etiology except during the postoperative period.

Chronic inflammation of the anterior segment tends to be granulomatous. Signs that indicate a chronic course include band keratopathy, iris atrophy, iris neovascularization, peripheral anterior synechiae, and fibrotic posterior synechiae.[48] Pigmented KPs on the corneal endothelium and pigmented clumps on the anterior lens capsule also suggest a recurrent or chronic course.

Pigmented cells may mimic inflammatory white blood cells in the AC and lead to an erroneous diagnosis of anterior uveitis. In patients with a "white eye" and no ocular signs or symptoms of uveitis, noninflammatory causes such as benign noninflammatory pigment should be considered. Anterior uveitis in a "white eye" may also be caused by JIA and FHI.

Diagnosis and work-up

Performing a basic anterior uveitis workup with additional tailored diagnostic testing based on history and

physical examination improves diagnostic efficiency while minimizing patient harm and resource use.[9,10,45,49,50] All investigations should be guided by a thorough medical history, review of systems, ophthalmic examination, and systemic evaluation. In cases of diagnostic uncertainty, workup should be oriented toward etiologies that are treatable or associated with high morbidity.

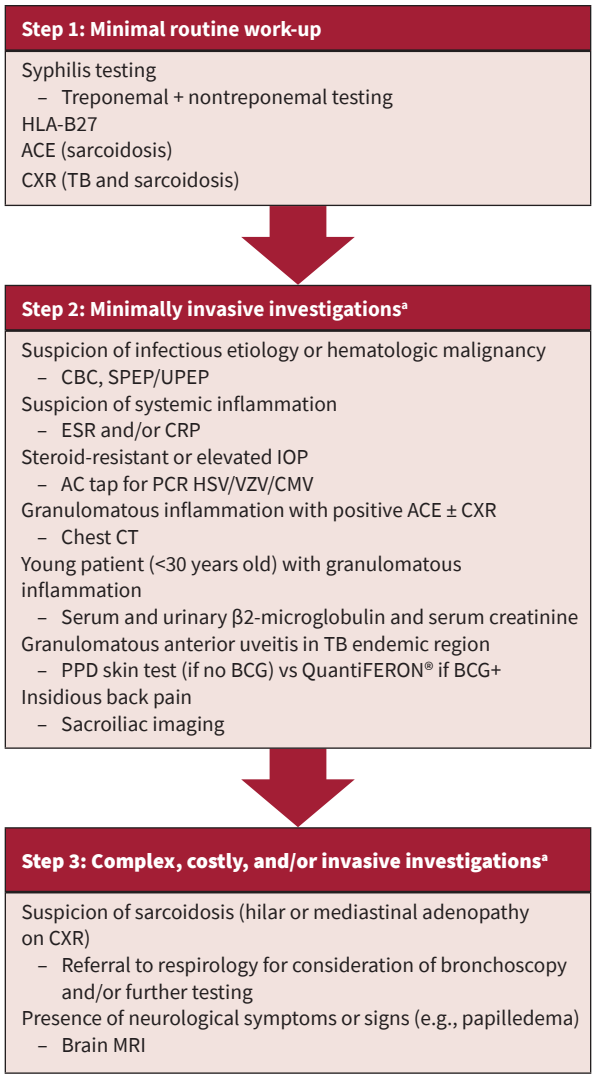
Based on previous consensus recommendations and the regional epidemiology of anterior uveitis, we outline a stepwise approach to diagnostic work-up in Figure 1.[9,10,45,50] The only case of anterior uveitis that does not require workup is a healthy patient who presents with a first, non-severe episode that fits the classical picture of an idiopathic etiology (i.e., acute, unilateral, non-granulomatous).[9,45] The first step in workup is a set of routine investigations that should be obtained in all patients, including syphilis testing (treponemal/nontreponemal testing), HLA-B27, serum angiotensin-converting enzyme (ACE), and chest X-ray (CXR). Basic bloodwork such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) should be ordered on a case-by-case basis due to their low specificity.[51,52]

The second step of workup involves pursuing minimally invasive investigations based on medical history and clinical findings. High suspicion of a viral infection (i.e., acute, unilateral, high IOP with or without corneal involvement) should prompt an AC tap with polymerase chain reaction testing for viruses in the herpes family.[53] In patients with chronic or granulomatous anterior uveitis and either positive ACE or CXR, a chest computerized tomography (CT) should be considered to further assess for sarcoidosis. In adult patients with anterior uveitis who are systemically well, antinuclear antibody (ANA) and antineutrophilic cytoplasmic antibody (ANCA) levels should not be performed. Granulomatous uveitis in a young patient (<30 years) should prompt consideration of tubulointerstitial nephritis and uveitis (TINU) and warrants investigation with serum creatinine and serum and urine β2-microglobulin.[54] In the case of TB, a skin test or interferon-γ release assay (IGRA) should be performed with any of the following: uveitis in a patient from a TB-endemic area or high-risk population, granulomas on CXR, granulomatous anterior uveitis, or severe nongranulomatous uveitis that requires treatment with systemic immunosuppression. Infectious etiologies should always be ruled out in patients who are immunocompromised, hospitalized, and recent recipients of surgery. Finally, obtain sacroiliac imaging in patients with insidious back pain to assess for spondyloarthropathy.

The vast majority of nonidiopathic anterior uveitis etiologies will be found within the first 2 steps of the workup strategy.[49,50] The third step entails complex, costly, and/or invasive investigations that may be considered when diagnostic uncertainty remains and specific disease entities are suspected. Neoplastic causes are very rarely thought to be the culprit (e.g., typical presentation in an older patient with steroid-resistant treatment), a CBC, serum and urine protein electrophoresis as well as a diagnostic paracentesis can be obtained and sent for cytology. If sarcoidosis is suspected based on serology and chest imaging, a referral to a respirologist for further workup is recommended. Any patient who concomitantly presents with neurological symptoms or signs should be further assessed with neuroimaging and/or lumbar puncture. Other investigations that are pursued in the absence of clinical findings are likely to be low yield.[9,10,45,50]

Evidence on the diagnostic utility of uveitis investigations comprises mostly retrospective studies with limited sample sizes. The ULISSE study is the only randomized controlled trial to have investigated different diagnostic approaches.[49] Among 676 adult patients with undifferentiated uveitis, a stepwise workup strategy achieved a similar proportion of diagnoses and involved half as many complementary investigations as an open, unrestricted method. This finding was consistent across anatomically divided subgroups. A subsequent cost-consequence analysis found that the mean healthcare cost per patient was significantly lower in the standardized group for anterior uveitis.[55] The investigations with the highest diagnostic yield were HLA-B27, ACE, TB skin test, IGRA, CXR, chest CT, and sacroiliac imaging.[50] More than 98% of HLA-B27-positive cases were anterior uveitis, indicating the low value of HLA-B27 testing in intermediate and posterior uveitis. Other bloodwork such as CBC, ESR, CRP, serum chemistries, liver enzymes, intracellular serologies, and bacterial serologies were rarely contributive.[49] Furthermore, immunologic testing never led to a diagnosis. The clinical yield of more complex and invasive investigations (e.g., vitrectomy, cerebral magnetic resonance imaging, bronchoscopy) were difficult to interpret due to small sample sizes but ranged from 15.9% to 66.7%.[49] The main limitation of ULISSE

Figure 1. Tailored, stepwise strategy for etiological workup of anterior uveitis[9,10,45,50]



[a]Choice of investigations should be based on history of presenting illness, review of systems, physical examination findings, and results of previous testing.
AC, Anterior chamber; ACE, angiotensin-converting enzyme; BCG, Bacillus Calmette–Guérin vaccine; CBC, complete blood count; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computerized tomography; CXR, chest x-ray; ESR, erythrocyte sedimentation rate; HSV, herpes simples virus; HLA, human leukocyte antigen; IOP, intraocular pressure; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PPD, purified protein derivative; SPEP, serum protein electrophoresis TB, tuberculosis; UPEP, urine protein electrophoresis; VZV, varicella zoster virus

was that the intervention arm had a significantly higher prevalence of women and acute anterior uveitis, whereas the comparator group had a higher proportion of recurrent and posterior uveitis.

A few investigations have high diagnostic value in select cases. ACE has excellent specificity for sarcoidosis,[56] but specificity is decreased in younger individuals and results are not interpretable in patients on ACE inhibitors. For anterior uveitis in children, ANA and rheumatoid factor (RF) may be obtained to further characterize JIA. From an imaging perspective, positron emission tomography scans have higher diagnostic value for sarcoidosis in older patients (>50 years) with posterior synechiae and hilar or mediastinal adenopathy on CXR.[57]

Management

The goal of uveitis treatment is to achieve sustained, corticosteroid-free remission. Overall, management should follow a stepladder, algorithmic approach where treatment is titrated based on severity and advanced when less aggressive modalities are intolerable or ineffective at reducing inflammation.[58] In the acute stage, establishing prompt control of inflammation is important for decreasing structural damage associated with visual morbidity.

Corticosteroids remain the mainstay of therapy in this phase due to their potent anti-inflammatory effects; however, their long-term use may be limited primarily by IOP elevation and cataract formation.[59] Corticosteroids should be started at a high dose and subsequently tapered based on clinical response. Typically, a gradual taper with a decrease of 1 drop daily per week should be implemented to reduce the risk of flaring and rebound. Topical corticosteroids administered between a few times daily to hourly are usually sufficient for achieving quiescence with anterior uveitis. In acute and severe cases, as well as patients with poor compliance or treatment response, periocular corticosteroids may be given.[45] The risk of cataract and secondary glaucoma increases with each injection.[60] Systemic corticosteroids may be used for severe unilateral or bilateral cases that are treatment-resistant to topical therapy or secondary to systemic disease with parallel indications. An expert panel in Taiwan suggested that anterior uveitis flares become concerning when they occur more than 3 times a year and thus may require systemic immunomodulatory therapy (IMT) to decrease the burden of topical therapy.[45] Finally, sustained-release corticosteroid implants may be considered in severe anterior uveitis cases that are intolerant of topical corticosteroids or systemic IMT. IMT is still ideally needed in these cases because of the risks associated with long-term corticosteroid use.[61]

Topical cycloplegic agents are often used in conjunction with corticosteroids. These agents reduce photophobia and pain by relaxing ciliary body spasm. Furthermore, they release posterior synechiae and prevent their development, which also reduces the risk of angle-closure glaucoma.[45]

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are mainly used as an adjunct with topical corticosteroids. These agents can be helpful in reducing postoperative anterior uveitis and uveitic cystoid macular edema. Systemic NSAIDs are generally not used in the primary treatment of anterior uveitis.

In general, IMT can be considered in cases of anterior uveitis that have a severe or sight-threatening course; respond poorly or are refractory to corticosteroids (i.e., require more than 2 drops per day of topical prednisolone 1% acetate to achieve inflammatory control); or develop severe IOP elevation in response to topical corticosteroids. IMT is also indicated in cases involving systemic inflammatory disease that necessitate systemic treatment, such as HLA-B27 associated spondyloarthritis (Table 2).[45,58,62] Indications for IMT should be balanced with behavioural (e.g., noncompliance), systemic (e.g., liver disease), and reproductive (e.g., pregnancy) risks.[62] Classes of IMT include antimetabolites, biologics (e.g., tumor necrosis factor inhibitors, anti-interleukin agents, anti-CD20), inhibitors of T-lymphocyte signaling and alkylating agents.[45,62] Antimetabolites such as methotrexate (ocular dosing 20-25 mg/week) are typically used as a first-line agent, followed by adalimumab as a first-line biologic. Ophthalmologists should feel comfortable co-managing these cases with a rheumatologist and directing them with appropriate ocular dosing. Thorough baseline investigations and routine bloodwork done every 3 months are required while taking these medications.

IMT typically elicits a therapeutic response within 3 months of treatment initiation, during which an immunosuppressive bridge should be used. Strong indicators of therapeutic response include visual acuity and severity of ocular inflammation.[1] If the treatment effect is inadequate at the maximum tolerated dose it is always helpful to reassess your diagnosis and reconsider the history, review of systems, and physical examination. Address the potential for nonadherence to medication. If none of these factors are contributory, the activity is likely due to inadequate therapy and the IMT should be escalated with an agent from a different class. On the other hand, if an IMT regimen has achieved corticosteroid-free remission, dosing should be kept constant for at least 2 years before attempting a taper.[58]

Surgical intervention is usually reserved for uveitis-related complications, mainly glaucoma and cataract. Uncontrolled glaucoma requiring surgical intervention may require therapeutic options, including gonioscopy-assisted transluminal trabeculotomy, insertion of drainage devices such as Ahmed glaucoma valves, or trabeculectomy. Early referral to a glaucoma specialist is crucial and glaucoma surgery should be performed ideally after more than 3 months of uveitis quiescence to reduce postoperative complications.[58] Similarly, cataract surgery should be performed once uveitis is stable. In cases of neovascularization of the iris or trabecular meshwork angle, vascular endothelial growth factor inhibitors can be injected off-label.[63,64]

For infectious anterior uveitis, management comprises a combination of local corticosteroid therapy and systemic antimicrobial therapy that targets the causative pathogen. Periocular corticosteroid administration should generally be avoided in infectious uveitis. When a specific infectious etiology is strongly suspected, it is reasonable to administer prophylactic antimicrobial therapy before diagnostic confirmation.[65]

Table 2. Indications to initiate systemic IMT for noninfectious anterior uveitis[45,58,62]

- Active (>5 cell/hpf) despite very frequent (q1h) and prolonged course of topical corticosteroids
- Inactive uveitis but requiring frequent topical steroid use to maintain quiescence (>bid of topical prednisolone 1%)
- Severe steroid responder limiting topical steroid use to adequately control uveitis
- Multisystem inflammatory disease that requires systemic IMT; e.g., active ankylosing spondylitis and uveitis

hpf, high-powered field; IMT, immunomodulatory therapy

Conclusion

Anterior uveitis is the most common anatomical form of uveitis and can lead to sight-threatening sequelae if it is not properly managed. Due to the multitude of potential presentations and etiologies, characterization of the disease requires a thorough review of symptoms and a multisystem examination. Diagnostic workup is crucial for treatment and should follow a tailored, stepwise approach that is guided by medical history, clinical findings, and regional epidemiology. Investigations that are obtained in the absence of clinical orientation are often of limited utility and incur significant costs to patients and the healthcare system. Most cases of anatomically isolated anterior uveitis will resolve with topical corticosteroids and cycloplegic agents, but some etiologies require escalation of therapy to include topical NSAIDs and systemic IMT. Visual prognosis hinges on targeted treatment. Further population-based studies with rigorous methodology are needed to elucidate the epidemiology of anterior uveitis in Canada.

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Mr. Xie is a medical student, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario. **Dr.** Kaplan is a Lecturer, Department of Ophthalmology and Vision Sciences, University of Toronto, and a Staff Ophthalmologist, Toronto Western Hospital, University Health Network, Toronto, Ontario.

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