CHAPTER 5

Diagnostic Considerations in Uveitis

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Highlights

- Uveitis refers to a heterogeneous set of diseases characterized by intraocular inflammation that may be infectious or noninfectious in origin and may be associated with a systemic disease or limited to the eye. Worldwide, uveitis is a leading cause of vision loss and visual impairment.
- Ocular inflammatory diseases with similar clinical features may differ in terms of treatment and prognosis, so accurate diagnosis is crucial.
- A formalized uveitis nomenclature uses clinical and anatomical features to describe, categorize, and grade intraocular inflammation.
- The differential diagnosis of uveitis is generated from the patient history, review of systems, and targeted systemic examination in combination with characteristics of the ocular inflammation.
- Laboratory workup and other ancillary testing for uveitis are tailored to the patient and the disease characteristics.

Overview

The uvea (also called the *uveal tract*) is a pigmented and vascular layer of the eye that includes the iris, ciliary body, and choroid. The dark purple choroid resembles a grape; hence, the term *uvea* was derived from the Latin word *uva,* meaning grape. Although the technical definition of *uveitis* is inflammation of the uvea, the clinical manifestation of uveitic diseases is intraocular inflammation that may include non-uveal ocular structures such as the vitreous, optic nerve, and retina. One of the hallmarks of intraocular inflammation is the presence of visible cells in the aqueous and/or vitreous humor. Other manifestations of intraocular inflammation, such as retinal vasculitis and macular edema, may require

ophthalmic imaging for detection. Inflammation can also involve other structures of the eye, such as the cornea (keratitis), sclera (scleritis), extraocular muscles (myositis), and orbit (orbital inflammation or orbital pseudotumor). The evaluation and treatment of *non-uveitic* ocular inflammatory disease (eg, scleritis) shares similarities with the approach for uveitis.

The term *uveitis* does not indicate etiology. Uveitis refers to a heterogeneous set of diseases that may be noninfectious (presumed to have an autoimmune or autoinflammatory origin), or that may be caused by infectious organisms. In addition, infectious and noninfectious uveitis can be isolated or associated with systemic disease. Uveitis that is isolated to the eye and noninfectious is considered an autoimmune disease that affects only the eye(s) and may be called *undifferentiated,* or *idiopathic,* uveitis.

When uveitis is suspected, the initial patient evaluation includes careful assessment of the anatomical location and characteristics of the ocular inflammation. Multimodal ophthalmic imaging has an important role in characterizing intraocular inflammation. A detailed patient history and review of systems are essential for gathering evidence of possible associated systemic disease. Limited examination of pertinent nonocular organ systems might be indicated by the review of systems or uveitis differential diagnosis. Further investigations should be guided by the ophthalmic findings in the context of the history and systemic signs or symptoms. Laboratory studies can help determine the etiology of intraocular inflammation; however, they are never a substitute for a thorough history and review of systems. An incomplete or inappropriate workup can delay diagnosis, lead to incorrect treatment, and have disastrous effects on ophthalmic and systemic prognoses. See Chapter 6 for an extensive discussion of uveitis treatment options.

Epidemiology

Uveitis is responsible for approximately 10% of blindness in the United States and Europe and up to 25% of blindness worldwide. The prevalence of uveitis is 58–121 cases per 100,000 people in the United States and reaches 730 cases per 100,000 people in the developing world. Anterior uveitis is the most common type of uveitis, representing 70%–80% of cases, followed by panuveitis, posterior uveitis, and intermediate uveitis. Women have slightly higher rates of uveitis overall. Although most surveys show that the incidence of uveitis peaks in people between 20 and 60 years of age, recent data suggest that the risk of uveitis is also increased in people older than 65 years. In general, the prevalence of uveitis is about five- to tenfold lower in children than in adults. Developing countries have higher rates of infectious uveitis, posterior uveitis, and panuveitis than industrialized nations. Certain types of uveitis are also associated with geographic region or origin, such as birdshot chorioretinopathy in western Europe, Behçet disease in Turkey and China, and tuberculosis-associated uveitis in India.

Acharya NR, Tham VM, Esterberg E, et al. Incidence and prevalence of uveitis: results from the Pacific Ocular Inflammation Study. *JAMA Ophthalmol.* 2013;131(11):1405–1412.

Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California: the Northern California Epidemiology of Uveitis Study. *Ophthalmology.* 2004;111(3):491–500.

Rathinam SR, Krishnadas R, Ramakrishnan R, et al; Aravind Comprehensive Eye Survey Research Group. Population-based prevalence of uveitis in Southern India. *Br J Ophthalmol.* 2011;95(4):463–467.

Rim TH, Kim SS, Ham D, Yu S, Chung EJ, Lee SC; Korean Uveitis Society. Incidence and prevalence of uveitis in South Korea: a nationwide cohort study. *Br J Ophthalmol*. 2018;102(1):79–83.

Thorne JE, Suhler E, Skup M, et al. Prevalence of noninfectious uveitis in the United States: a claims-based analysis. *JAMA Ophthalmol*. 2016;134(11):1237–1245.

Classification of Uveitis

In 2005, several international societies developed a universal method for describing uveitis, called the *Standardization of Uveitis Nomenclature (SUN)* system. This classification system, which is based on the anatomical location of inflammation and specific descriptors of its onset, duration, and course, has since been accepted by uveitis specialists worldwide. As mentioned in the overview, uveitis is divided into noninfectious (autoimmune/autoinflammatory) and infectious conditions, and by the presence or absence of associated systemic manifestations. Uveitis is classified anatomically by the SUN system, which includes 4 subcategories: (1) anterior uveitis, (2) intermediate uveitis, (3) posterior uveitis, and (4) panuveitis. Table 5-1 reviews these 4 groups. Of note, if both anterior chamber and vitreous inflammatory cells are present but the amount of vitreous inflammation is more than expected for an isolated anterior uveitis, the classification should be "anterior and intermediate uveitis" and not "panuveitis." Posterior uveitis or panuveitis must include choroidal and/or retinal lesions.

The SUN system further refines the anatomical classification of uveitis with descriptors based on clinical onset, duration, and course (Table 5-2). Terminology for grading and monitoring uveitic activity was also developed (Table 5-3). In 2021, the SUN system established additional criteria for classifying 25 specific types of uveitis, which are discussed elsewhere in Section 9.

Table 5-1 Anatomical Classification of Uveitis Based on Standardization of Uveitis Nomenclature (SUN) Criteria

Type	Primary Site of Inflammation	Includes
Anterior uveitis	Anterior chamber	Iritis Iridocyclitis Anterior cyclitis
Intermediate uveitis	Vitreous	Pars planitis Posterior cyclitis Hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal, or diffuse choroiditis Chorioretinitis Retinochoroiditis Retinitis Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	

Reproduced with permission from Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of nomenclature for reporting clinical data: results of the First International Workshop. *Am J Ophthalmol.* 2005;140(3):510.

Table 5-2 Descriptors of Uveitis Based on Standardization of Uveitis Nomenclature (SUN) Criteria

Category	Descriptor	Comment
Onset	Sudden	
	Insidious	
Duration	Limited	≤3 months' duration
	Persistent	>3 months' duration
Course	Acute	Episode characterized by sudden onset and limited duration
	Recurrent	Repeated episodes separated by periods of inactivity without treatment ≥3 months in duration
	Chronic	Persistent uveitis with relapse in <3 months after discontinuing treatment

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Table 5-3 Uveitis Terminology Based on Standardization of Uveitis Nomenclature (SUN) Criteria

Term	Definition
Inactive	Grade 0 cells (anterior chamber)
Worsening activity	Two-step increase in level of inflammation (eg, anterior chamber cells, vitreous haze) or increase from grade 3+ to 4+
Improved activity	Two-step decrease in level of inflammation (eg, anterior chamber cells, vitreous haze) or decrease to grade 0
Remission	Inactive disease for ≥3 months after discontinuing all treatments for eye disease

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Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data: results of the First International Workshop. *Am J Ophthalmol.* 2005;140(3):509–516.

Anatomical Classification

Anterior uveitis

Anterior uveitis produces inflammatory signs predominantly in the anterior chamber as a result of inflammation of the iris and ciliary body. Inflammation confined to the anterior chamber is also called *iritis;* when there are cells in the retrolental (anterior vitreous) space, it can be called *iridocyclitis*. When more than one ocular structure is involved, the convention is to name the primary site of inflammation first; for example, *sclerokeratitis* is keratitis that develops in association with scleritis. Inflammatory processes that originate in the cornea with secondary involvement of the anterior chamber are called *keratouveitis.* An inflammatory reaction that involves the sclera and uveal tract is called *sclerouveitis*.

Severe or chronic anterior uveitis may produce secondary structural complications such as corneal edema, band keratopathy, iris abnormalities, cataract, uveitic macular edema, and optic disc swelling. These complications are not part of the formal classification system but may facilitate disease recognition and therapy decisions. It is important to understand that the presence of posterior segment complications such as macular edema does *not* indicate that the anatomical classification is posterior uveitis or panuveitis; as discussed previously, inflammatory lesions must be present in the choroid or retina in posterior uveitis or panuveitis. Chapter 8 discusses anterior uveitis in greater detail.

Intermediate uveitis

In intermediate uveitis, inflammation is most prominent in the vitreous cavity. Vitritis results from inflammation of the ciliary body, retinal vasculature, pars plana, and/or peripheral retina. Clinical signs include vitreous haze and cellular debris that is often associated with peripheral or diffuse retinal vascular leakage. Macular edema is the most common structural complication of intermediate uveitis; severe or chronic disease may cause peripheral exudative or tractional detachments, retinal neovascularization, cataract, or retrolental membrane formation. The diagnostic term *pars planitis* refers to a subset of intermediate uveitis in which there are peripheral preretinal collections of exudative and inflammatory debris in the absence of an associated infection or systemic disease. See Chapter 8 for further discussion of intermediate uveitis.

Posterior uveitis

Posterior uveitis is defined as intraocular inflammation involving primarily the retina and/or choroid. Inflammatory cells may be observed diffusely throughout the vitreous cavity, overlying foci of active chorioretinal inflammation, or on the posterior vitreous face. Ophthalmoscopy reveals focal, multifocal, or diffuse areas of retinitis and/or choroiditis, often with retinal vasculitis. Different types of posterior uveitis may have a similar clinical appearance, although some clinical patterns of disease are nearly pathognomonic for diagnosis. Structural complications such as macular edema, epiretinal membrane, and retinal or choroidal neovascularization are not sufficient for the anatomical classification of posterior uveitis. Chapters 9–12 discuss noninfectious and infectious posterior uveitis in greater detail.

Panuveitis

In panuveitis, inflammation is present in all anatomical divisions of the eye without a predominantly affected site. The inflammation may be associated with an infectious or noninfectious systemic disease. See also Chapters 10–12, which discuss noninfectious and infectious panuveitis, and Chapter 14, which covers endophthalmitis.

Retinal vasculitis

Retinal vasculitis is defined by the presence of retinal vascular changes in association with ocular inflammation. The term *retinal vasculitis* is used in distinction to *vasculopathy,* in which there are vessel changes but no visible evidence of inflammation. On fluorescein angiography studies, retinal vasculitis encompasses perivascular sheathing, vascular leakage, or occlusion. Peripheral vascular sheathing may be observed in intermediate uveitis, but it is not sufficient for the anatomical classification of posterior uveitis/panuveitis. Retinal vasculitis is not

Table 5-4 Diseases With Retinal Vasculitis

Primarily Arteritis	Primarily Phlebitis	Arteritis and Phlebitis
Systemic lupus erythematosus	Sarcoidosis	Ocular toxoplasmosis
Polyarteritis nodosa	Multiple sclerosis	Relapsing polychondritis
Syphilis	Behçet disease	Granulomatosis with polyangiitis
HSV, VZV (ARN/BARN)	Birdshot chorioretinopathy	Crohn disease
HSV, VZV (PORN)	HIV paraviral syndrome	Frosted branch angiitis
IRVAN	Eales disease	
Churg-Strauss syndrome		
Susac syndrome		

ARN = acute retinal necrosis; BARN = bilateral acute retinal necrosis; HSV = herpes simplex virus; IRVAN = idiopathic retinal vasculitis, aneurysms, and neuroretinitis; PORN = progressive outer retinal necrosis; VZV = varicella-zoster virus.

Adapted from Foster CS, Vitale AT. *Diagnosis and Treatment of Uveitis.* 2nd ed. Jaypee Brothers Medical Publishers; 2012:123–128.

considered a defining feature for the anatomical classification of any type of uveitis. Table 5-4 summarizes diseases associated with retinal vasculitis.

Classification by Clinical Features

Certain types of uveitis have stereotyped clinical patterns; recognizing and labeling these patterns can aid in obtaining the correct uveitis diagnosis. The SUN system is useful for describing onset, duration, and course of uveitis, as summarized in Table 5-2. The severity of the inflammation may also influence categorization and prognosis. For example, the inflammatory process may occur in one or both eyes, or it may alternate between them. The clinical appearance, size, and distribution of lesions—especially chorioretinal lesions and keratic precipitates—are also used to describe uveitis. Naming conventions for descriptive terms are discussed in the Signs of Uveitis section that follows.

Uveitis can be clinically described as granulomatous or nongranulomatous; however, these descriptions do not necessarily correlate with the *histologic* appearance and may be influenced by the disease stage, the amount of antigen at presentation, or the treatment stage (eg, after initiation of corticosteroid treatment). In addition, uveitis may present with granulomatous features that eventually appear nongranulomatous with chronicity or treatment. Histologically, *granulomatous* inflammation is characterized by epithelioid and giant cells; clinically, granulomatous uveitis may include large, predominantly inferior, clumped keratic precipitates or nodular or creamy deposits in the iris, vitreous, optic nerve, and/or choroid. In contrast, *nongranulomatous* inflammation typically has a lymphocytic and plasma cell infiltrate; clinically, nongranulomatous uveitis is characterized by smaller keratic precipitates that are distributed diffusely, but uveal deposits are absent.

Discrete histologic granulomas are characteristic of sarcoidosis and tuberculosis, and diffuse clinical granulomatous inflammation appears in Vogt-Koyanagi-Harada syndrome and sympathetic ophthalmia. Viral anterior uveitis may present with a granulomatous or nongranulomatous appearance. Zonal histologic granulomatous disease can be observed in lens-induced uveitis.

Symptoms of Uveitis

Symptoms produced by uveitis depend on the site of uveal tract inflammation, the rapidity of onset, the duration of the disease, the course of the disease, and sometimes the underlying etiology.

Depending on the etiology and severity of inflammation, the presentation of anterior uveitis may range from an asymptomatic white eye to an extremely painful red eye. Sudden-onset anterior uveitis usually causes acute eye pain and redness, photophobia, and blurred vision. Pain results from ciliary spasm associated with iris inflammation and may radiate over the larger area served by the fifth cranial nerve (the trigeminal nerve). Intraocular pressure (IOP) elevation due to angle closure or trabeculitis can also cause pain.

In contrast, in patients with juvenile idiopathic arthritis, chronic anterior uveitis may not be associated with any symptoms at all. Even when patients are initially asymptomatic, however, chronic or severe anterior uveitis can cause blurred vision because of structural complications such as calcific band keratopathy, cataract, or macular edema.

Isolated intermediate uveitis presents with a white, quiet eye and produces symptoms of floaters and blurred vision. Floaters result from the shadows cast by vitreous cells and debris on the retina. Blurred vision can result from macular edema or vitreous opacities in the visual axis.

In patients with posterior uveitis, presenting symptoms include painless blurred vision, floaters, photopsias, scotomas, metamorphopsia, nyctalopia, or a combination of these symptoms. The blurred vision is caused primarily by retinitis and/or choroiditis directly affecting macular function or secondarily by complications of inflammation such as macular edema. Table 5-5 summarizes the symptoms of uveitis.

Signs of Uveitis

The chemical mediators involved in inflammation (see Chapter 1) result in vascular dilation (ciliary flush), increased vascular permeability causing migration of proteins into the eye (aqueous flare in the anterior segment), and chemotaxis of inflammatory cells into the eye (aqueous and vitreous cellular reaction). Table 5-6 summarizes the ocular findings that may be seen in uveitis.

Table 5-5 Symptoms of Uveitis

Acute Anterior Segment Inflammation	Posterior Segment Inflammation
Redness	Floaters
Pain	Photopsias
Photophobia	Scotomas (central or peripheral)
Epiphora	Metamorphopsia
Blurred vision[a]	Nyctalopia
	Blurred vision[a]

[a] Blurred vision may occur because of refractive shift; blockage from inflammatory cells; cataract; calcific band keratopathy; macular edema; retinochoroiditis; or corneal, macular, or optic disc edema.
Note: Some subsets of uveitis may have no symptoms.

Table 5-6 Findings Associated With Uveitis

Eyelid and skin
- Vitiligo
- Nodules
- Ptosis/eyelid edema

Conjunctiva or sclera
- Injection
  - Perilimbal (ciliary flush)
  - Diffuse or sectoral
  - Episcleral or scleral
- Nodules
- Scleral thinning

Corneal endothelium
- Keratic (cellular) precipitates (diffuse or inferior cornea)
- Fibrin
- Pigment (nonspecific)

Anterior chamber
- Cells
- Aqueous flare (proteinaceous influx)
- Pigment (nonspecific)

Iris
- Nodules
- Posterior synechiae
- Atrophy
- Heterochromia

Angle
- Peripheral anterior synechiae
- Nodules
- Vascularization

Intraocular pressure
- Hypotony
- High pressure
- Trabeculitis or secondary glaucoma

Vitreous
- Cells (single or clumped)
- Haze (proteinaceous influx)
- Traction bands

Pars plana
- Snowbanks

Retina
- Thickening and/or whitening (retinitis, infiltrate, ischemia, necrosis)
- Inflammatory cuffing of vessels (sheathing)
- Neovascularization
- Edema
- Macular edema
- Epiretinal membranes
- Subretinal fluid
- Retinal pigment epithelium: hypertrophy, clumping, or loss

Choroid
- Inflammatory infiltrate/thickening
- Atrophy
- Neovascularization

Optic nerve
- Edema (nonspecific)
- Neovascularization
- Pallor

Anterior Segment

Signs of uveitis and structural complications in the anterior portion of the eye include

- inflammatory cells (Fig 5-1)
- aqueous flare (Fig 5-2)
- hypopyon
- fibrin in the anterior chamber
- keratic precipitates (Figs 5-3, 5-4)
- iris nodules (Fig 5-5)
- iris atrophy or heterochromia
- pupillary miosis
- synechiae, anterior and posterior (Fig 5-6)
- pigment dispersion
- cataract (more likely in chronic uveitis than in acute disease)
- band keratopathy (more likely in chronic uveitis than in acute disease)

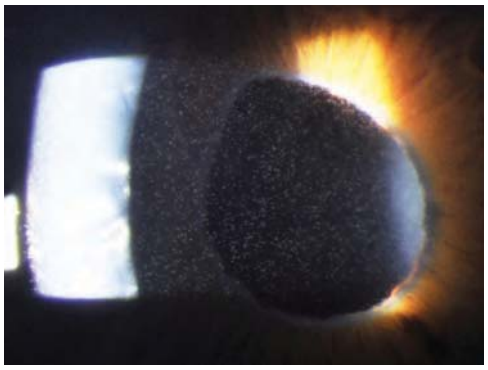

Figure 5-1 Inflammatory cells in the anterior chamber (grade 4+) of a patient with anterior uveitis. *(Courtesy of Emmett T. Cunningham Jr, MD, PhD, MPH.)*

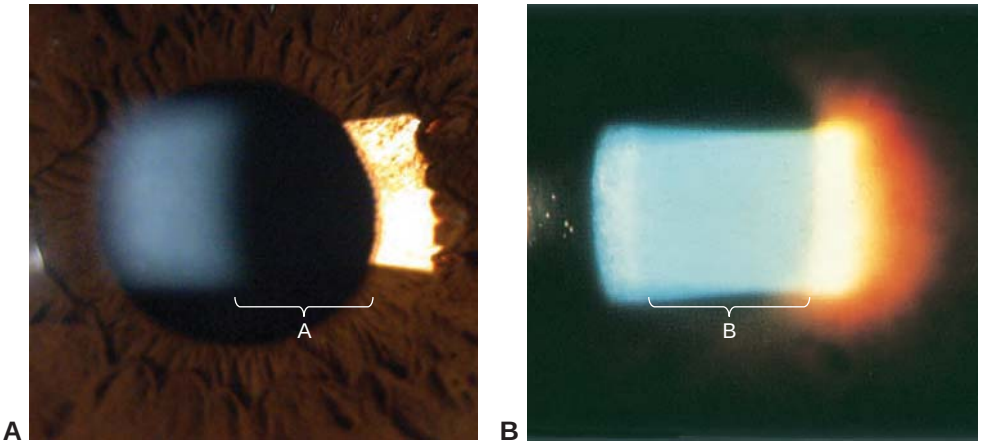

Figure 5-2 Appearance of the slit-lamp beam when grading aqueous flare. **A,** In a healthy eye with no aqueous flare, the anterior chamber is optically empty, creating an interrupted appearance of the light beam. **B,** In a severely inflamed eye, aqueous proteins scatter light, creating a continuous appearance of the beam (4+ flare). *(Part A courtesy of Zachary A. Koretz, MD, MPH.)*

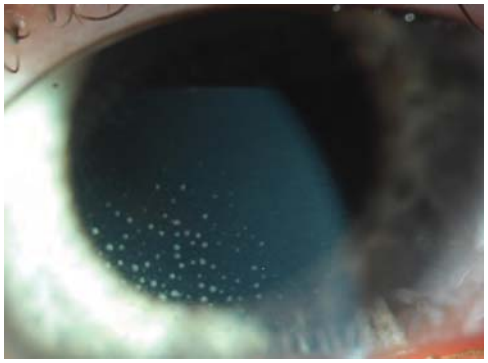

Figure 5-3 Keratic precipitates (medium and small). *(Courtesy of Debra A. Goldstein, MD.)*

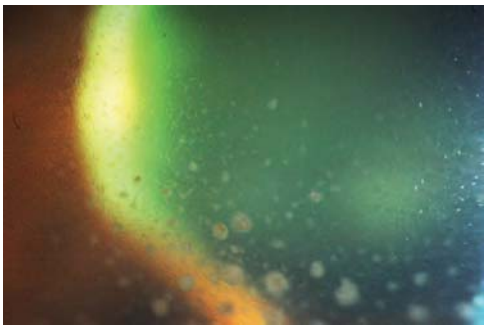

Figure 5-4 Large "mutton-fat" keratic precipitates in a patient with sarcoidosis. Large keratic precipitates such as these may be associated with a granulomatous disease process. *(Courtesy of Debra A. Goldstein, MD.)*

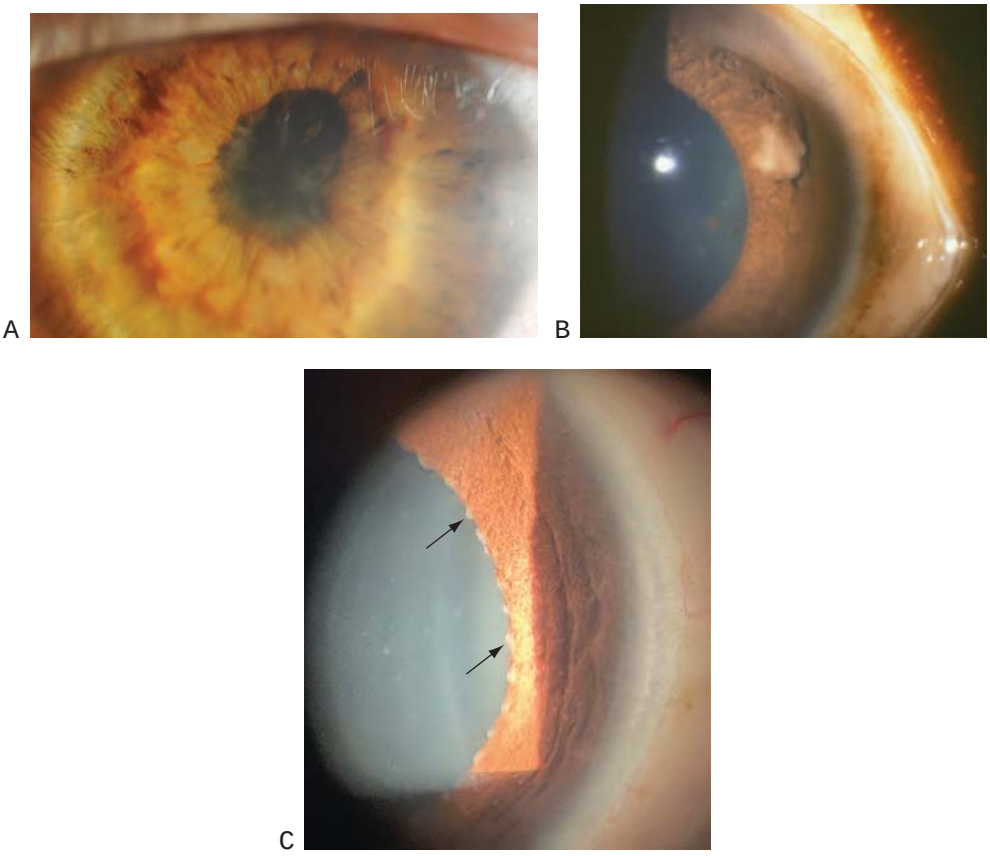

Figure 5-5 **A, B** Mid-iris nodules (Busacca nodules) in two patients with sarcoidosis. **C,** Nodules on pupil margin (Koeppe nodules; *arrows highlight 2 of them*) in another patient with sarcoidosis. *(Part A courtesy of Debra A. Goldstein, MD; part B courtesy of Wendy M. Smith, MD; and part C courtesy of Sam S. Dahr, MD, MS.)*

The major finding in anterior uveitis is the presence of inflammatory cells and flare in the anterior chamber, but there may be many additional sequelae (see the preceding list). The SUN system grades anterior chamber cells according to the number of inflammatory cells observed on slit-lamp examination in a field defined as a 1×1-mm high-power

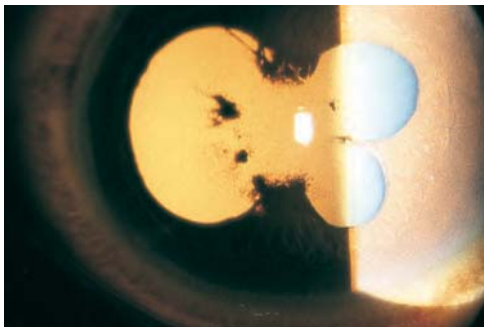

Figure 5-6 Multiple posterior synechiae preventing complete dilation of the pupil. *(Courtesy of David Forster, MD.)*

Table 5-7 Grading Scheme for Anterior Chamber Cells and Flare Based on Standardization of Uveitis Nomenclature (SUN) Criteria

Grade	Number of Cells (High-Intensity 1 × 1-mm Slit Beam)	Flare
0	<1	None
0.5+	1–5	Not applicable
1+	6–15	Faint
2+	16–25	Moderate (clear iris details)
3+	26–50	Marked (hazy iris details)
4+	>50	Intense (fibrin or plasmoid aqueous)

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(16×–20×) beam at full intensity at a 45°–60° angle in a dark room. For the cell grade of 0.5+, there must be at least 1 cell per high-power field in each of the 4 anterior chamber quadrants. Flare is defined by the visibility of the slit-lamp beam in the anterior chamber. The SUN system adopted the flare grading method described previously by Hogan and colleagues (Table 5-7).

The anterior chamber reaction can be described as follows:

- serous (aqueous flare caused by proteinaceous influx)
- purulent (polymorphonuclear leukocytes and necrotic debris causing hypopyon)
- fibrinous (plasmoid or intense fibrinous exudate)
- sanguinoid (inflammatory cells with erythrocytes, as manifested by hypopyon mixed with hyphema)

Keratic precipitates (KPs), collections of inflammatory cells on the corneal endothelium, are described by

- size: small, medium, or large
- morphology: fine, round, nummular, stellate, granulomatous, mutton-fat
- distribution: diffusely over entire corneal endothelium, settled in a gravity-dependent triangular pattern in the inferior cornea *(Arlt triangle),* or focal and associated with corneal inflammation

Newly formed KPs tend to be white and smoothly rounded, later becoming crenated (shrunken), pigmented, or glassy in nature. Large, yellowish KPs are called *mutton-fat KPs* and are usually associated with granulomatous types of inflammation. Small stellate KPs distributed diffusely on the cornea are usually associated with Fuchs uveitis syndrome or herpetic anterior uveitis. Associated corneal edema may also be present. Band keratopathy is seen in chronic uveitis (especially juvenile idiopathic arthritis associated).

Iris involvement may manifest as either anterior or posterior synechiae, iris nodules (Koeppe nodules at the pupillary border, Busacca nodules within the iris stroma [see Fig 5-5], and Berlin nodules in the angle), iris granulomas, heterochromia (eg, Fuchs uveitis syndrome), or stromal atrophy (eg, herpetic uveitis).

With uveitic involvement of the ciliary body and trabecular meshwork, IOP is often low, secondary to decreased aqueous production or increased uveoscleral outflow; however, IOP may increase precipitously if the meshwork becomes clogged by inflammatory cells or debris or if the trabecular meshwork itself is the site of inflammation (ie, trabeculitis, characteristically in herpetic uveitis). Pupillary block with iris bombé and secondary angle closure may also lead to an acute rise in IOP.

Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of uveitis: I. Anterior uveitis. *Am J Ophthalmol.* 1959;47(5, part 2):155–170.

Intermediate Segment

Signs of uveitis and structural complications in the intermediate portion of the eye include

- inflammatory cells in vitreous
- vitreous haze (Fig 5-7)
- snowballs (clumped inflammatory cells in vitreous)
- snowbanks (exudate over pars plana)
- ciliary body detachment
- retrolental membrane
- vitreous strands or traction band

The hallmark of intermediate uveitis is vitreous cells and haze. Cells may be clumped or individual. Vitreous haze is due to proteinaceous vitreous debris. Vitreous cells can be present without haze.

The physician typically grades vitreous cells on a 0–4 numeric scale by observing the retrolental space in a dilated eye using the slit-lamp biomicroscope and a 1×0.5-mm beam (Fig 5-8). The consensus is that cells in the vitreous strands are old, and cells in the syneretic areas are most likely new. Of note, the SUN system does not specify a grading system for vitreous cells. Table 5-8 shows the vitreous cell grading scale used in the Multicenter Uveitis Steroid Treatment Trial (MUST).

Vitreous haze may be a better indicator of disease activity than cell counts alone. The grading of vitreous haze is based on the clarity of view of the posterior segment on ophthalmoscopic examination using an indirect ophthalmoscope and a 20 D lens. The National Institutes of Health grading system for vitreous haze, adopted by the SUN system, uses a standardized set of fundus photographs that defines vitreous haze on a 0–4 scale (see Fig 5-7).

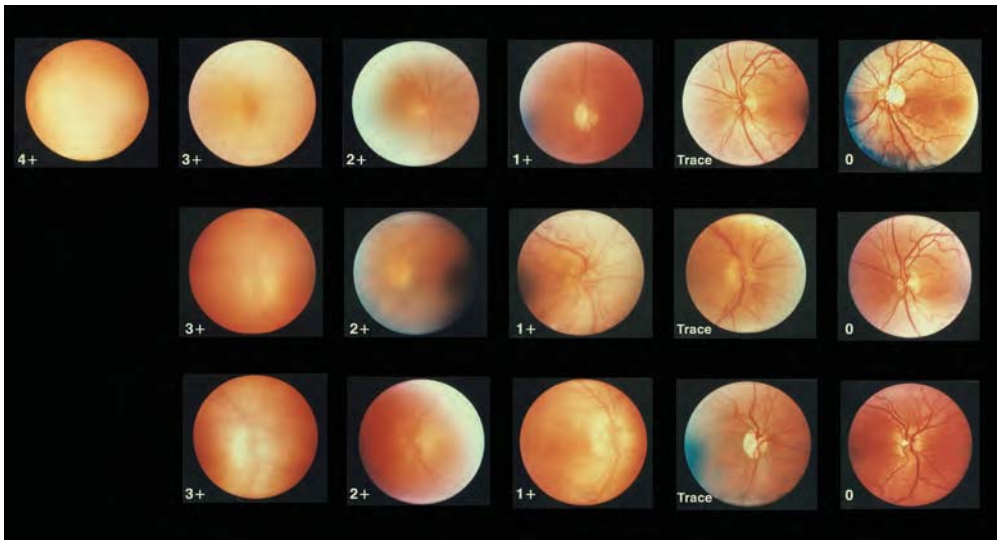

Figure 5-7 Grading scale for vitreous haze: representative standard images. Grade 4: Dense opacity obscuring optic nerve head. Grade 3: Optic nerve visible, borders blurred, no retinal vessels seen. Grade 2: Optic nerve and retinal vessels substantially blurred but still visible. Grade 1: Few opacities, mild blurring of optic nerve and retinal vessels. Trace (0.5+): Trace. Grade 0: Clear. *(Courtesy of National Eye Institute; originally published in Nussenblatt RB, Palestine AG, Chan CC, et al. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis.* Ophthalmology. *1985;92(4):467–471.)*

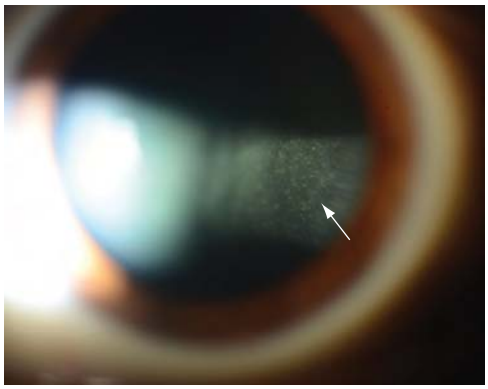

Figure 5-8 Slit-lamp photograph of vitreous cells *(arrow)* in the retrolental space of an inflamed eye. *(Courtesy of Emilio M. Dodds, MD.)*

Table 5-8 Grading Scheme for Vitreous Chamber Cells and Haze

Grade	Number of Cells in Retrolental Space (High-Intensity 1 × 0.5-mm Slit Beam)	Vitreous Haze
0	0	Clear view of fundus
0.5+	1–5	Not applicable
1+	6–10	Faint
2+	11–20	Moderate (clear optic nerve details)
3+	21–50	Marked (hazy optic nerve details)
4+	>50	Intense (minimal/no optic nerve detail)

Vitreous haze has been used as inclusion criteria in clinical trials for uveitis, and a 2-step improvement in haze has been used as a principal outcome measure.

Additional signs of inflammation in the vitreous include *snowball opacities* (clumps of inflammatory cells in the vitreous) and *snowbanks* (exudates over the pars plana, especially prominent inferiorly). Active snowbanks have a fluffy or shaggy appearance. As pars planitis becomes inactive, the pars plana appears gliotic or fibrotic and smooth; thus, these changes are not referred to as *snowbanks.* Vitreous strands and snowballs may also vary in clinical appearance by disease type. Chronic intermediate uveitis may be associated with cyclitic membrane formation, secondary ciliary body detachment, and hypotony.

Posterior Segment

Signs of uveitis and structural complications in the posterior segment of the eye include the following:

- retinal or choroidal inflammatory infiltrates
- inflammatory sheathing of arteries or veins
- perivascular hemorrhage
- exudative, tractional, or rhegmatogenous retinal detachment
- retinal pigment epithelial hypertrophy or atrophy
- atrophy or swelling of the retina, choroid, or optic nerve head
- preretinal or subretinal fibrosis
- retinal or choroidal neovascularization

Posterior segment inflammation is a result of inflammatory or infectious infiltration of the retina and choroid. Retinal and choroidal signs may be unifocal, multifocal, or diffuse. Lesions are described by size, color, morphology, and anatomical relationship to posterior pole landmarks. Some active lesions may exhibit blurred margins, transitioning to sharply defined and/or pigmented borders when inactive.

Chorioretinal lesion morphology may be described as follows:

- punched out: round with well-demarcated borders
- placoid: large, flat, gray-white lesions with patchy distribution and indistinct margins
- serpentine: lesions with sharply defined wavy borders

Altaweel MM, Gangaputra SS, Thorne JE, et al. Morphological assessment of the retina in uveitis. *J Ophthalmic Inflamm Infect*. 2016;6(1):33. doi:10.1186/s12348-016-0103-2

Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology.* 1985;92(4):467–471.

Review of the Patient's Health and Other Associated Factors

When uveitis is suspected, a comprehensive patient history and review of systems help to narrow the differential diagnosis and guide ancillary testing and treatment options. The patient's personal characteristics, medical history, and social history can help in the

Table 5-9 Patient Factors in the Diagnosis of Uveitis

Patient Characteristics	Family and Social History	Additional Modifying Factors
Age	Family or personal history of autoimmune disease/endemic infection	Immunization history
Sex	Intravenous drug use	Immune system status
Genetic traits, and sometimes race, ethnicity and/or country of origin	Tobacco exposure	Systemic medications
	Occupation	Trauma history
	Sexual practices	Travel history
	Eating habits	Hospital admissions/surgery
	Animal exposures	Indwelling lines/instrumentation
		Review of systems and existing medical conditions

classification and identification of uveitis (Table 5-9). Immunocompromise, sexual practices, use of intravenous drugs, hyperalimentation, and certain occupations are some examples of the risk factors that can direct the investigation. In this regard, the diagnostic survey for uveitis shown in Appendix A may be very helpful.

Although ocular inflammation can be an isolated process involving only the eye, it can also be associated with a systemic condition. However, uveitis frequently does not correlate with inflammatory activity elsewhere in the body and may precede the development of inflammation at other body sites.

Differential Diagnosis of Uveitis

The differential diagnosis of uveitis includes infectious diseases due to a variety of agents (viruses, bacteria, fungi, protozoa, and helminths), noninfectious entities of presumed immunologic origin, and unknown causes (called *idiopathic* or *undifferentiated uveitis*). In addition, masquerade syndromes such as vitreoretinal lymphoma, retinoblastoma, leukemia, choroidal metastases, and malignant melanoma may be mistaken for uveitis. Other relevant masquerade syndromes include juvenile xanthogranuloma, pigment dispersion syndrome, retinal detachment, vitreous hemorrhage, retinitis pigmentosa, and ocular ischemic syndrome. Each of these masquerade syndromes should be considered in the differential diagnosis of uveitis. See Chapter 15 for further discussion of masquerade syndromes.

A careful patient history and accurate description of ophthalmoscopic findings are extremely helpful in narrowing the differential diagnosis, as certain presentations are characteristic for specific diseases. However, many patients do not present with the classic signs and symptoms of uveitis, or their clinical appearance may evolve with time and treatment. In these cases, the clinician should still rely on the tools of classification based on anatomical location and associated factors (eg, acute versus chronic, unilateral versus bilateral, adult versus child) to narrow the differential to the uveitic entities that share the patient's characteristics. See Table 5-10 for a simplified version of one system for narrowing the differential diagnosis. Activity 5-1 provides a decision-tree algorithm for the evaluation of a patient with uveitis.

Table 5-10 Simplified Scheme for Patient Evaluation in Uveitis

Type of Inflammation	Possible Associated Factors	Suspected Disease[a]	Ancillary Tests and Consultations
		Anterior Uveitis	
Acute/sudden onset, severe with or without fibrin membrane or hypopyon	Arthritis, back pain, GI/GU symptoms	Seronegative spondyloarthritis (ankylosing spondylitis, reactive arthritis, inflammatory bowel disease, psoriatic arthritis)	HLA-B27; sacroiliac films; rheumatology, gastroenterology referrals
	Oral and genital ulcers, skin findings	Behçet disease	Clinical diagnosis, screen for other organ involvement; rheumatology referral
	Febrile illness, flank or abdominal pain	TINU syndrome	Renal function tests, urinalysis, urine β_2-microglobulin; nephrology referral
	Postsurgical or penetrating eye trauma or systemic indwelling lines/instrumentation/infection	Infectious endophthalmitis, toxic anterior segment syndrome	B-scan for vitritis, consider vitreous culture, vitrectomy For endogenous endophthalmitis, consider blood cultures and systemic infectious workup
	None	Undifferentiated (idiopathic)	HLA-B27
Moderate severity (red, painful)	Shortness of breath, skin findings, granulomatous inflammation	Sarcoidosis	ACE, lysozyme; CXR/chest CT; biopsy
	Blunt eye trauma	Traumatic iritis	
	Increased IOP	Glaucomatocyclitic crisis, herpetic iritis If pseudophakic, uveitis-glaucoma-hyphema syndrome	Clinical diagnosis; PCR of intraocular fluid[b] optional
	Poor response to steroids	Syphilis	Syphilis IgG or FTA-ABS or MHA-TP followed by RPR or VDRL test
	Postsurgical	Low-grade endophthalmitis (eg, *Cutibacterium acnes*); IOL related	Consider vitrectomy, capsulectomy with culture

Type of Inflammation	Possible Associated Factors	Suspected Disease[a]	Ancillary Tests and Consultations
		Anterior Uveitis *(continued)*	
Chronic (minimal redness, pain)	Child, especially with arthritis	JIA-associated anterior uveitis	ANA, ESR, RF; rheumatology referral
	Heterochromia or small nodules, diffuse KPs, unilateral	Fuchs uveitis syndrome	Clinical diagnosis
	Postsurgical	Low-grade endophthalmitis (eg, *C acnes*); IOL related	Consider vitrectomy, capsulectomy with culture
	None	Undifferentiated	
		Intermediate Uveitis	
Mild to moderate	Shortness of breath, skin findings, granulomatous inflammation	Sarcoidosis	ACE, lysozyme; CXR/chest CT; biopsy
	Tick exposure, erythema chronicum migrans rash, endemic area	Lyme disease (may also be anterior uveitis, posterior/panuveitis)	ELISA, Western blot for confirmation
	Neurologic symptoms	Multiple sclerosis	MRI of brain and C-spine; LP for oligoclonal bands; neurology referral
	Older than 50 years	Vitreoretinal lymphoma	Vitrectomy; chorioretinal biopsy; cytology; IL-10:IL-6 ratio[b]; *MYD88* mutation, genotyping studies; brain MRI, LP
	None	Pars planitis	
		Posterior Uveitis	
Chorioretinitis with vitritis			
Focal	Adjacent scar; ingestion of raw meat, unwashed vegetables, endemic area	Toxoplasmosis	Clinical diagnosis; negative serology to rule out the diagnosis; PCR of intraocular fluid[b] optional
	Child; history of geophagia	Toxocariasis	Clinical diagnosis; ELISA, complete blood count with differential
	HIV infection or immunosuppressed	CMV retinitis (variable vitritis)	PCR of intraocular fluid[b]
Multifocal	Shortness of breath, skin findings	Sarcoidosis	ACE, lysozyme; CXR/chest CT; biopsy
	TB-endemic area	TB	IGRA or PPD, CXR/chest CT
	Peripheral retinal necrosis with occlusive arteriolar vasculitis	ARN	PCR of intraocular fluid[b]; possibly vitrectomy/retinal biopsy

(Continued)

Table 5-10 *(continued)*

Type of Inflammation	Possible Associated Factors	Suspected Disease[a]	Ancillary Tests and Consultations
		Posterior Uveitis *(continued)*	
	HIV infection or immunosuppressed	Syphilis, toxoplasmosis	Syphilis IgG or FTA-ABS or MHA-TP and RPR or VDRL test; *Toxoplasma* serology
	IV drug use, indwelling lines	*Candida, Aspergillus* infection	Blood, vitreous cultures
	Visible intraocular parasite, patient origin from Africa or Central/South America	Cysticercosis Onchocerciasis	ELISA, brain MRI Skin snip
	Older than 50 years	Vitreoretinal lymphoma	Vitrectomy; chorioretinal biopsy cytology; IL-10:IL-6 ratio[b]; *MYD88* mutation, genotyping studies; brain MRI, LP
	None	Birdshot chorioretinopathy Multifocal choroiditis with panuveitis	Clinical diagnosis; HLA-A29 Rule out TB, sarcoidosis, syphilis
Diffuse	Dermatologic/CNS symptoms; serous retinal disease; no history of ocular surgery or penetrating ocular trauma	Vogt-Koyanagi-Harada syndrome	Clinical diagnosis; LP to document CSF pleocytosis; consider audiology referral
	Postsurgical/traumatic, bilateral, serous retinal disease	Sympathetic ophthalmia	
	Postsurgical/traumatic, unilateral	Infectious endophthalmitis	Consider vitrectomy, culture
	Child; history of geophagia	Toxocariasis	ELISA; complete blood count with differential
Unilateral	Warm climate; host animal exposures	DUSN: early disease has gray, clustered lesions and vitritis; late findings are diffuse RPE degeneration, waxy disc pallor, attenuated arterioles	Clinical diagnosis; visualization of nematode

Type of Inflammation	Possible Associated Factors	Suspected Disease[a]	Ancillary Tests and Consultations
Posterior Uveitis *(continued)*			
Chorioretinitis *without* vitritis			
Focal	None; history of carcinoma	Neoplastic masquerade	Metastatic workup
Multifocal	Ohio/Mississippi Valley	Ocular histoplasmosis	Clinical diagnosis
	Lesions confined to posterior pole	White dot syndromes (eg, APMPPE, MEWDS, PIC)	Clinical diagnosis
	Serpentine or maplike pattern of scars	Serpiginous choroiditis	IGRA or PPD; CXR
Diffuse	From Africa, Central/South America	Onchocerciasis	Skin snip
	Severe immunocompromise (eg, AIDS)	Progressive outer retinal necrosis	Same as for ARN
Vasculitis			
	Aphthous ulcers, hypopyon	Behçet disease	Clinical diagnosis, screen for other organ involvement; rheumatology referral
	Malar rash, female, arthralgias	Systemic lupus erythematosus	ANA, anti-dsDNA, C3, C4; rheumatology referral
	Chronic sinusitis with hemorrhagic rhinorrhea, dyspnea, renal insufficiency, purpura	Granulomatosis with polyangiitis	c-ANCA (anti–proteinase 3); rheumatology referral
Panuveitis			
See entities described earlier in the table: sarcoidosis, Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, Behçet disease, syphilis, toxoplasmosis, endophthalmitis, toxocariasis, and cysticercosis.			

ACE = angiotensin-converting enzyme; ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA antibody; APMPPE = acute posterior multifocal placoid pigment epitheliopathy; ARN = acute retinal necrosis; c-ANCA = cytoplasmic antineutrophil cytoplasmic antibody; CMV = cytomegalovirus; CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; CXR = chest x-ray; DUSN = diffuse unilateral subacute neuroretinitis; ELISA = enzyme-linked immunosorbent assay; ESR = erythrocyte sedimentation rate; FTA-ABS = fluorescent treponemal antibody absorption test; GI = gastrointestinal; GU = genitourinary; HLA = human leukocyte antigen; IgG = immunoglobulin G; IGRA = interferon-gamma release assay; IL = interleukin; IOL = intraocular lens; IOP = intraocular pressure; IV = intravenous; JIA = juvenile idiopathic arthritis; KP = keratic precipitate; LP = lumbar puncture; MEWDS = multiple evanescent white dot syndrome; MHA-TP = microhemagglutination assay–*Treponema pallidum;* MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PIC = punctate inner choroidopathy; PPD = purified protein derivative; RF = rheumatoid factor; RPE = retinal pigment epithelium; RPR = rapid plasma reagin; TB = tuberculosis; TINU = tubulointerstitial nephritis and uveitis.

[a] Syphilis may present as any type of uveitis and should be considered in all patients.

[b] Testing where available.

ACTIVITY 5-1 Flowchart for clinical diagnosis and treatment of uveitis: simplified interactive tool.
Activity developed by Thellea K. Leveque, MD, MPH.

Ancillary Testing

Medical history, review of systems, thorough ophthalmologic and general physical examinations, and formulation of a working differential diagnosis are cornerstones of the workup of a patient with uveitis. Once a list of differential diagnoses has been compiled on the basis of anatomical location and clinical characteristics of the inflammation, the ophthalmologist can order appropriate laboratory tests. A "shotgun" approach to a uveitis workup (eg, ordering laboratory tests without consideration of a reasonable differential) is expensive and may yield confusing results, which may not be related to the uveitis but will still require further evaluation to rule out clinical significance. Laboratory testing is not a substitute for a thorough, hands-on clinical evaluation.

Regarding ancillary testing, *no standardized battery of tests is appropriate for all patients with uveitis.* Rather, a tailored testing approach should be based on the most likely causes of ocular inflammation in each case. Many patients will require only a few diagnostic tests.

Most uveitis specialists do recommend syphilis testing for all patients with uveitis because syphilis can present as any form of ocular inflammation and systemic infection is often undiagnosed. In addition, if a patient with occult syphilis infection is treated with only corticosteroids, the systemic and ophthalmic outcomes can be disastrous. In the appropriate clinical scenario or when systemic immunomodulatory therapy will be used, most uveitis specialists also recommend testing for tuberculosis. A chest radiograph can also screen for sarcoidosis, which is a common cause of uveitis with protean manifestations. Table 5-11 lists some of the laboratory tests and imaging studies used in uveitis evaluations, as well as their indications. Later chapters also discuss these tests according to types of uveitis.

CLINICAL PEARL

There is no accepted "uveitis workup" or standard workup that is appropriate for all of the various types of uveitis. Use the review of systems and the examination findings to define the differential diagnosis. Based on the differential, select diagnostic testing and imaging to rule in or rule out diagnoses. A "shotgun" approach to a uveitis workup (eg, ordering laboratory tests without consideration of a reasonable differential) is expensive and may yield confusing results that are not related to the uveitis but still require further evaluation to confirm the lack of clinical significance.

It is important to use caution not only when ordering laboratory tests but also when interpreting their results, as even very sensitive and specific tests can yield misleading results if the likelihood of disease in a particular patient is low. In other words, when a large group of patients are tested for a very rare disease, a positive test result may not represent the true presence of disease. The Bayes theorem, a statistical calculation used to determine

Table 5-11 Laboratory Tests and Imaging Studies Used in Uveitis Evaluations or Medication Monitoring

Test	Indications and/or Potential Diagnoses
Hematologic blood tests	
Complete blood count with differential	Baseline or monitoring for IMT and select antibiotics/antivirals Leukemia, lymphoma, immune status (eg, neutropenia)
Erythrocyte sedimentation rate	Giant cell arteritis, nonspecific systemic inflammation
Interferon-gamma release assay	Latent and active tuberculosis
T-cell subsets	Opportunistic infection, HIV
Serologic tests	
Liver function tests (ALT, AST)	IMT monitoring (antimetabolites) Sarcoidosis, hepatitis
Serum urea nitrogen, creatinine	IMT monitoring (T-cell inhibitors) Interstitial nephritis
Angiotensin-converting enzyme, lysozyme, calcium	Sarcoidosis
Antinuclear antibody	Connective tissue disease, juvenile idiopathic arthritis
Antiphospholipid antibodies	Vasculitis, vascular occlusion
Rheumatoid factor, anti-citrullinated protein antibody	Rheumatoid arthritis, juvenile idiopathic arthritis
HLA testing	
HLA-B27	Spondyloarthritis, acute anterior uveitis
HLA-A29	Birdshot chorioretinopathy
HLA-B51 (rarely obtained and of limited value)	Behçet disease (*not* required for diagnosis)
HLA-DRB1*01:02	TINU syndrome
ANCA testing—c-ANCA (proteinase 3) and p-ANCA (myeloperoxidase)	Systemic vasculitides
Syphilis IgG/FTA-ABS/MHA-TP (treponemal tests); followed by reflex VDRL/RPR (nontreponemal tests)	Syphilis
Lyme disease serology	Lyme disease
Brucella species serology	Brucellosis
Toxoplasma gondii serology	Toxoplasmosis
Fungal serology (complement fixation), (1→3)-β-D-glucan assay	Coccidioidomycosis, typically not obtained for presumed ocular histoplasmosis; nonspecific fungal infection
Bartonella quintana and *Bartonella henselae* serology	Cat-scratch disease
EBV, HSV, VZV, CMV serology	Viral uveitis (little benefit unless negative)
HIV serology/Western blot	HIV/AIDS, opportunistic infections, vascular occlusions

(Continued)

Table 5-11 *(continued)*

Test	Indications and/or Potential Diagnoses
CSF studies	
Protein, glucose, cell counts/cytology, cultures, Gram stain, CSF VDRL, oligoclonal bands	APMPPE (if magnetic resonance imaging evidence of central nervous system vasculitis), VKH syndrome, syphilis and other infection, malignancy, vitreoretinal lymphoma, multiple sclerosis
Urine studies	
Urinalysis for hematuria, proteinuria, and casts; urinary β_2-microglobulin	IMT monitoring (cyclophosphamide toxicity) ANCA-associated vasculitides, TINU syndrome
Radiographic studies	
Chest radiography	Tuberculosis, sarcoidosis, granulomatosis with polyangiitis
Sacroiliac joint x-rays	Spondyloarthritis
Computed tomography of chest	Tuberculosis, sarcoidosis, granulomatosis with polyangiitis
Computed tomography/magnetic resonance imaging of brain and orbits	Sarcoidosis, central nervous system lymphoma, toxoplasmosis, APMPPE, multiple sclerosis
Intraocular fluid analysis and tissue biopsy	
Polymerase chain reaction	Viridae: HSV-1, HSV-2, VZV, CMV, EBV, Ebola, Zika, West Nile, rubella Bacteria: universal 16S subunit for pan bacteria; individual polymerase chain reaction primers available for many individual bacteria, varies by laboratory Protozoa: *Toxoplasma gondii* Fungi: universal 18S or 28S subunit for pan fungi: *Candida albicans, Aspergillus* species (28S rRNA gene) Vitreoretinal lymphoma (IgH, TCR, *MYD88,* others)
Endoretinal, subretinal, choroidal biopsy	Necrotizing retinitis, neoplasia (vitreoretinal lymphoma, metastasis)
Skin, conjunctival, lacrimal biopsy	Sarcoidosis, infection, lymphoma, amyloidosis
Stool for detection of pathogenic microorganisms	Parasitic diseases; viruses, bacteria, fungi

ALT = alanine aminotransferase; ANCA = antineutrophil cytoplasmic antibody; APMPPE = acute posterior multifocal placoid pigment epitheliopathy; AST = aspartate aminotransferase; c-ANCA = cytoplasmic ANCA; CMV = cytomegalovirus; CSF = cerebrospinal fluid; EBV = Epstein-Barr virus; FTA-ABS = fluorescent treponemal antibody absorption test; HLA = human leukocyte antigen; HSV = herpes simplex virus; IgG = immunoglobulin G; IgH = immunoglobulin heavy locus; IMT = immunomodulatory therapy; MHA-TP = microhemagglutination assay–*Treponema pallidum;* p-ANCA = perinuclear ANCA; RPR = rapid plasma reagin; rRNA = ribosomal ribonucleic acid; TCR = T-cell receptor; TINU = tubulointerstitial nephritis and uveitis syndrome; VDRL = venereal disease research laboratory; VKH = Vogt-Koyanagi-Harada; VZV = varicella-zoster virus.

the probability of an event based on prior knowledge of conditions that may be related to the event, describes this concept. See BCSC Section 1, *Update on General Medicine*.

McKay KM, Lim LL, Van Gelder RN. Rational laboratory testing in uveitis: a Bayesian analysis. *Surv Ophthalmol.* 2021;66(5):802–825.

Ophthalmic Imaging and Functional Tests

Ophthalmic imaging and functional testing are useful for diagnosis of uveitis as well as for monitoring the patient's response to therapy. In addition, these tests can provide information not obtainable from biomicroscopic or fundus examination. The use of combined imaging modalities, called *multimodal imaging,* can be complementary and additive in these tasks. For discussion of ophthalmic imaging modalities and electroretinography, see BCSC Section 12, *Retina and Vitreous*.

Kawali A, Pichi F, Avadhani K, Invernizzi A, Hashimoto Y, Mahendradas P. Multimodal imaging of the normal eye. *Ocul Immunol Inflamm.* 2017;25(5):721–731.

Van Gelder RN. Diagnostic testing in uveitis. *Focal Points: Clinical Modules for Ophthalmologists.* American Academy of Ophthalmology; 2013, module 4.

Optical coherence tomography

Optical coherence tomography (OCT), a noncontact imaging technique that produces a series of high-resolution cross-sectional images of the retina and choroid, is used to identify morphologic changes in eyes with uveitis. In addition, OCT has become the reference standard for objective measurement of uveitic macular edema (Fig 5-9), retinal thickening, subretinal and intraretinal fluid associated with choroidal neovascularization, serous retinal detachments, and chorioretinal lesions. Although OCT can be surprisingly useful in evaluating the macula in eyes with nondilating pupils, media opacity can limit its clarity. In addition, OCT is valuable in monitoring the nerve fiber layer in patients with uveitic glaucoma, and anterior segment OCT may be useful in evaluating an eye for retained lens fragments or intraocular lens (IOL) chafing in those with persistent postoperative uveitis. Efforts to develop objective OCT-based grading of intraocular cells/inflammation are also ongoing.

Enhanced depth imaging OCT (Fig 5-10) provides deeper tissue penetration than standard OCT. This technique allows visualization of the choroid, which can undergo structural alterations in several uveitic diseases, notably Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, and birdshot chorioretinopathy.

OCT angiography (OCTA) provides repeated high-resolution scans of the same area to assess differences in blood flow, producing structural images of perfused vessels in ocular tissues. OCTA can be useful in distinguishing between inflammatory lesions and choroidal neovascularization in the inflammatory retinochoroidopathies of unknown etiology (the *white dot syndromes*). Case reports and case series describing OCTA characteristics of active and inactive chorioretinal lesions are emerging. Over time, these may have increasing implications for the diagnosis and treatment of posterior uveitis entities.

Kim J, Knickelbein JE, Jaworski L, et al. Enhanced depth imaging optical coherence tomography in uveitis: an intravisit and interobserver reproducibility study. *Am J Ophthalmol.* 2016;164:49–56.

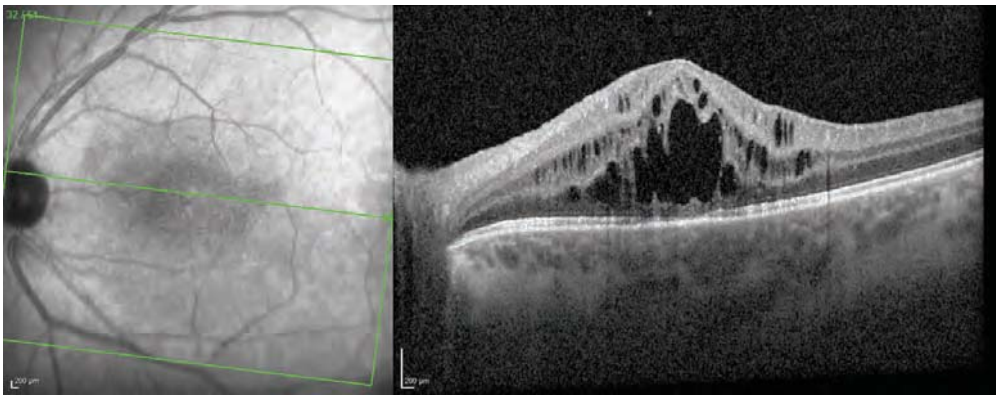

Figure 5-9 Optical coherence tomography (OCT) image of uveitic macular edema in a patient with juvenile idiopathic arthritis–associated uveitis. *(Courtesy of Thellea K. Leveque, MD, MPH.)*

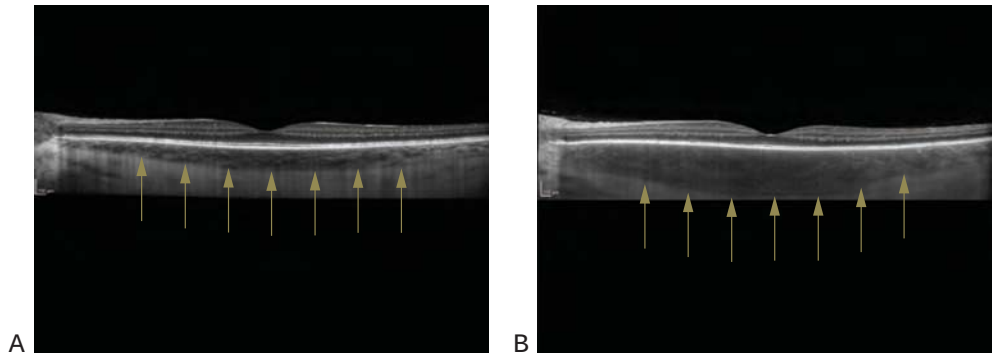

Figure 5-10 Enhanced depth imaging OCT in a patient with Vogt-Koyanagi-Harada syndrome. **A,** Relatively normal choroidal thickness *(arrows)* during quiescence. **B,** Massive, diffuse choroidal thickening *(arrows)* during active uveitis. *(Courtesy of Thellea K. Leveque, MD, MPH.)*

Pichi F, Sarraf D, Arepalli S, et al. The application of optical coherence tomography angiography in uveitis and inflammatory eye diseases. *Prog Retin Eye Res.* 2017;59:178–201.

Fluorescein angiography

Fluorescein angiography (FA) is an essential imaging modality for evaluating chorioretinal disease and structural complications caused by posterior uveitis. After intravenous injection of fluorescein sodium, a series of filtered posterior segment images provides functional and structural views of retinal (and to some degree choroidal) vasculature and anatomy. FA can also detect macular edema (Fig 5-11); retinal vasculitis; secondary choroidal or retinal neovascularization; and areas of optic nerve, retinal, and choroidal inflammation. In addition, several of the white dot syndromes have characteristic appearances on FA. Wide-field FA can identify retinal vascular pathology not visible on clinical examination.

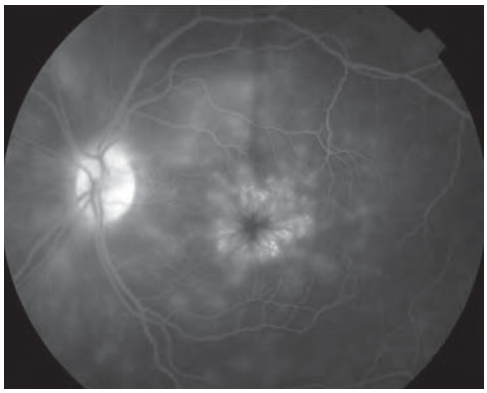

Figure 5-11 Late transit phase fluorescein angiogram of the left eye of a patient with sarcoidosis-associated anterior uveitis showing the petalloid pattern typical of uveitic macular edema. *(Courtesy of Ramana S. Moorthy, MD.)*

Laovirojjanakul W, Acharya N, Gonzales JA. Ultra-widefield fluorescein angiography in intermediate uveitis. *Ocul Immunol Inflamm.* 2019;27(3):356–361.

Color photography

Color photographs of the anterior or posterior segment can document lesion size, color, location, and morphologic characteristics and can be used to assess clinical progression or regression of disease, often in combination with other imaging modalities. These images can help establish a baseline when a relapsing and remitting inflammatory process is being assessed (eg, the presence of new posterior synechiae in anterior uveitis or transitory posterior segment inflammation characteristic of Behçet disease).

Fundus autofluorescence

Fundus autofluorescence imaging, another noninvasive technique for analyzing the posterior segment, maps the fluorescent property of lipofuscin, a breakdown product of retinal proteins, within the retinal pigment epithelium (RPE). This technique is useful in evaluating patients with posterior uveitis that involves the outer retina, RPE, and inner choroid. Hyperautofluorescence corresponds to increased metabolic activity of the RPE or window defect due to the loss of photoreceptors, whereas hypoautofluorescence occurs with loss or blockage of RPE cells. Although autofluorescence patterns vary between the different types of uveitis, in many cases, hyperautofluorescence occurs with increased disease activity and resolves or evolves to hypoautofluorescence as the inflammation subsides.

Indocyanine green angiography

Like FA, indocyanine green angiography (ICGA) uses an intravenous injection coupled with serial retinal images to provide data about vasculature and anatomy of the posterior segment; the properties of ICGA allow for specialized imaging of the choroidal circulation. In inflammatory diseases involving the outer retina and choroid, findings on ICGA often exceed those visible on either ophthalmoscopy or FA, which may have diagnostic and therapeutic implications. ICGA is especially beneficial in the evaluation of choroidal neovascular membrane as well as white dot syndromes (Fig 5-12), Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, and posterior segment sarcoidosis (see Chapters 9 and 10).

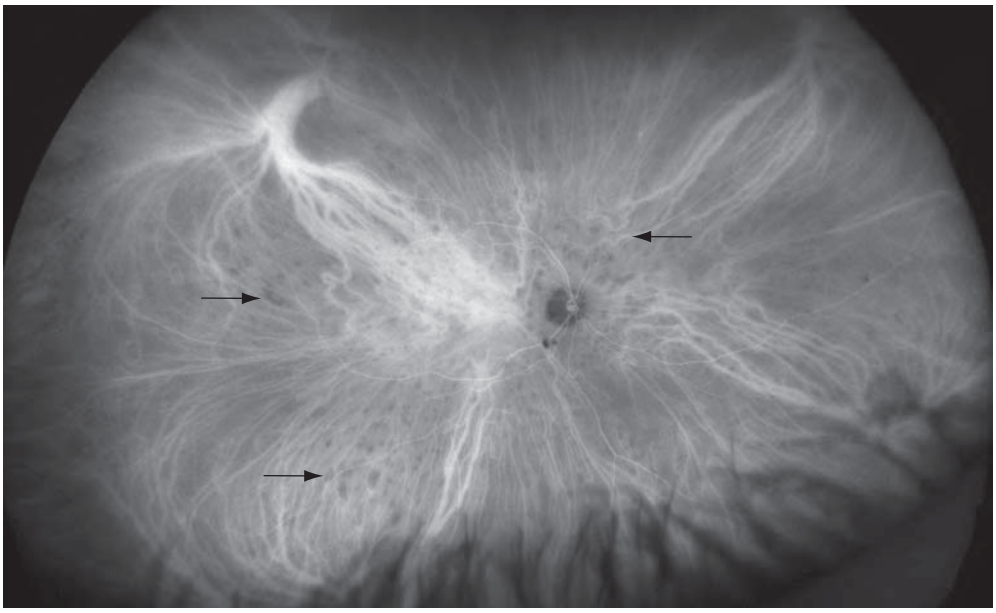

Figure 5-12 Wide-field image of late-phase indocyanine green angiography demonstrating numerous scattered hypocyanescent spots *(arrows)* in a patient with birdshot chorioretinitis. Eyelash artifact *(asterisk)* is also shown. *(Courtesy of Thellea K. Leveque, MD, MPH.)*

Ultrasonography

Anterior segment ultrasound biomicroscopy (UBM) can be useful in diagnosing pathology of the ciliary body, iris, and iridocorneal angle in uveitis. B-scan ultrasonography of the posterior segment can demonstrate vitreous opacities, choroidal thickening or elevation, retinal detachment, and cyclitic membrane formation, as well as rule out occult foreign bodies, particularly when media opacities preclude a view of the posterior segment. Retained crystalline lens fragments may be visualized in the anterior or posterior segment with either form of ultrasonography, whereas malposition of an IOL haptic can be demonstrated with anterior segment UBM. Findings on B-scan ultrasonography may be diagnostic for posterior scleritis (see Chapter 7).

Electroretinography

Full-field electroretinography can be used to monitor progression of birdshot chorioretinopathy and diagnose acute zonal occult outer retinopathy (AZOOR) complex diseases and autoimmune retinopathy. During uveitis workup, electroretinogram findings may help to distinguish retinal dystrophy from posterior uveitis.

Visual field testing (perimetry)

Kinetic and static perimetry are used to monitor progression and response to treatment of birdshot chorioretinopathy and AZOOR complex diseases. These tests are also used to monitor visual field defects in uveitic glaucoma and inflammatory optic neuritis. Microperimetry may be helpful in diseases involving the macula, such as punctate inner choroiditis.

Ocular Fluid and Tissue Sampling

Polymerase chain reaction testing of aqueous and vitreous humor

Polymerase chain reaction (PCR) testing is highly sensitive and specific for the diagnosis of infectious uveitis. For example, it can directly amplify the DNA of a suspected pathogen from a small volume of intraocular fluid, making it ideal for evaluation of ophthalmic disease. PCR-based techniques can also be very useful for vitreous genomic testing in suspected cases of vitreoretinal lymphoma.

Anterior chamber paracentesis is generally safer and easier to perform than vitreous sampling. Fortunately, viral PCR testing has high sensitivity and specificity for both aqueous and vitreous samples, but the diagnostic yield is affected by the clinical presentation. In cases of herpetic posterior uveitis or panuveitis (ie, acute retinal necrosis), aqueous and vitreous PCR results are nearly equally informative. In contrast, aqueous PCR may not be diagnostic in a patient with suspected viral anterior uveitis, especially if there is minimal inflammation when the aqueous is sampled. For *Toxoplasma* infection, aqueous PCR testing may also be less informative than vitreous testing unless the patient is immunocompromised or the retinochoroiditis lesions are large and/or multifocal.

Until recently, PCR analysis was not practical for the diagnosis of bacterial and fungal uveitis because of the need to specify the selected pathogen of interest for amplification. Due to the presence of conserved genetic subunits within bacteria (16S) and fungi (5.8S/18S/28S), pan-bacterial and pan-fungal PCR tests can be used to screen ocular specimens for these pathogens. The diagnostic yield of PCR assessments is equal or superior to that of intraocular fluid cultures.

When PCR testing of intraocular fluid is negative for a given infectious organism but clinical suspicion for the pathogen is still high, aqueous or vitreous biopsy may be repeated when inflammation is high grade or after antimicrobial treatment is discontinued. Disadvantages of PCR testing are cost, inability to test for multiple entities due to small sample size, risk of improper amplification of a contaminant, and risk of a false-negative result when there is a paucity of cellular material.

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Culture and vital staining

Cell culture and bacterial and fungal staining are useful in cases of suspected bacterial or fungal endophthalmitis. Isolation is time consuming, however, and may lack sensitivity

when the pathogen load in an ocular sample is small. Nevertheless, the technique remains the traditional first-line test for suspected infections, in part because it is widely available and inexpensive to perform.

Cytology and Pathology

Cytology studies of aqueous humor may be diagnostic in ocular diseases involving the anterior and sometimes the posterior segment (eg, leukemia or lymphoma). When there is clinical suspicion for vitreoretinal lymphoma, an undiluted vitreous biopsy specimen can be sent for cytology and flow cytometry analysis with gene rearrangement studies and cytokine analysis.

Although chorioretinal biopsy is technically challenging and requires an experienced vitreoretinal surgeon, it may be useful in rapidly progressive, vision-threatening types of posterior uveitis when other investigations have failed to identify an etiology and response to empiric treatment has been poor. Another indication for chorioretinal biopsy is suspected subretinal infiltration of vitreoretinal lymphoma in the absence of substantial vitreous cells or after a negative result from vitreous biopsy.

Directed conjunctival biopsy of visible lesions can be useful in lymphoma, cicatricial pemphigoid, and sarcoidosis. In rare cases, scleral biopsy may be indicated if suspicion is high for an infectious etiology (see Chapter 7).

In general, when the suspected disease involves nonocular organ systems, yield may be higher and morbidity lower with biopsy of a nonocular site versus a vitreous or chorioretinal biopsy.

Anterior chamber paracentesis technique

Paracentesis is performed using sterile technique at the slit lamp or with the patient supine on a treatment gurney or chair. Topical anesthetic drops are instilled, the eye is prepared with topical povidone-iodine solution, and an eyelid speculum can be placed. A tuberculin (1-mL) syringe is attached to a sterile 30-gauge needle, which is then advanced under direct or slit-lamp visualization into the anterior chamber through the temporal limbus or clear cornea, parallel to the iris plane. As much aqueous is aspirated as is safely possible (usually 0.1–0.2 mL), avoiding needle contact with the iris and lens. Possible complications include iris hemorrhage and hyphema, wound leak, infection, and injury to the iris or lens. Video 5-1 shows the anterior chamber paracentesis technique.

VIDEO 5-1 Anterior chamber paracentesis technique.
Courtesy of Thellea K. Leveque, MD, MPH.

Vitreous biopsy technique

The most common indications for vitreous biopsy include suspected vitreoretinal lymphoma or other intraocular malignancy, infectious posterior segment inflammation, and chronic uveitis with atypical presentation or inadequate response to therapy. (Endophthalmitis is discussed in detail in Chapter 14, and vitreoretinal lymphoma in Chapter 15.)

Vitreous specimens can be obtained via the pars plana either with a needle or a vitrectomy instrument. If only a small sample is required, a vitreous needle tap can be performed

with the patient partially reclining in an examination room chair. Topical and subconjunctival anesthesia are administered; the eye is then prepared with topical povidone-iodine solution, and an eyelid speculum is placed. Typically, a 25-gauge, 1-inch needle on a 3-mL syringe (to provide greater vacuum) is introduced through the pars plana, directed toward the midvitreous cavity, and used to aspirate the vitreous sample, usually 0.2–0.5 mL. A diagnostic vitrectomy is performed via a standard 3-port pars plana vitrectomy (see BCSC Section 12, *Retina and Vitreous*). Testing usually requires undiluted vitreous specimens. It is possible to obtain 0.5–1.0 mL of undiluted vitreous using standard vitrectomy techniques.

Complications of diagnostic vitrectomy in uveitic eyes may include retinal tears or detachment, suprachoroidal or vitreous hemorrhage, worsening of cataract or inflammation, and in rare cases, sympathetic ophthalmia. Although vitreous surgery can be therapeutic and diagnostic in cases of uveitis, the pharmacokinetics of intravitreal drugs are markedly altered in vitrectomized eyes; for example, the half-life of intravitreal corticosteroids is significantly reduced.

Chorioretinal biopsy technique

Video 5-2 demonstrates chorioretinal biopsy.

VIDEO 5-2 Chorioretinal biopsy.
Courtesy of P. Kumar Rao, MD.