

Diagnostic dilemmas in retinitis and endophthalmitis

JL Davis

Abstract

Visual loss in infectious posterior uveitis or panuveitis can occur if proper therapy is delayed because of diagnostic uncertainty. Some disorders, such as acute retinal necrosis and bacterial endophthalmitis, can be rapidly progressive, and therefore require prompt and accurate diagnosis to guide initial therapy. Other more slowly evolving infections, such as toxoplasmic chorioretinitis or fungal endophthalmitis, can be worsened by empiric use of corticosteroids without specific antimicrobial coverage. Key ocular diagnostic features are helpful but highly variable with overlap with both non-infectious uveitis and neoplastic masquerades, even for key signs such as hypopyon. Close examination of the fundus with attention to color, location, size, border, and opacity of lesions and associated arteriolitis or frosted branch angiitis is helpful in the diagnosis of chorioretinitis. Ultrasonography is an important tool in the evaluation of eyes with suspected endophthalmitis, especially those with intracapsular infection or focal infected deposits. Testing of intraocular fluid can be extremely useful but suffers from inaccessibility, poor sensitivity, and test selections dependent on a presumptive diagnosis, which may be wrong. The dilemma for clinician is to make the correct diagnosis of a rare, blinding, variegated disease quickly enough to intercede with specific therapy or to apply empiric therapy in a sufficiently skilled manner to avert disaster and confirm the diagnosis by response to treatment. When non-infectious uveitis is in the differential, empiric corticosteroids must sometimes be used, at great risk, if clinical examination, ancillary testing, and any available intraocular diagnostic tests have failed to confirm a diagnosis.

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Introduction

In 2008 the International Uveitis Study Group revised the original anatomic classification of uveitis to include only broad etiologic categories of infectious and non-infectious uveitis (as well as non-uveitic masquerades)¹ recognizing an essential dichotomy in intraocular inflammation. Infections involving the posterior segment have tremendous visual impact in individual cases, especially if treatment is mistakenly begun with injectable or oral corticosteroids. The clinician preparing to manage a significant intermediate, posterior, or panuveitis is therefore faced with an urgent diagnostic challenge. First, is this infectious or non-infectious uveitis? If infectious, is a bacteria, fungus, virus or other agent more likely to produce these clinical features? Finally, what is the urgency of empiric anti-infective treatment before confirmation of the final diagnosis?

Diagnostic challenges

For some cases of infectious uveitis infection is sufficiently obvious that it presents no diagnostic challenge. For example, pain, hypopyon, and reduced vision within 1–2 weeks of cataract extraction is assumed infectious, probably bacterial, and treated with intravitreal antibiotics. A confluent, 360° peripheral necrotizing retinitis in one or both eyes with or without immunocompromise should at least initially be suspected to be acute retinal necrosis (ARN) due to herpes simplex or varicella zoster and potentially rapidly progressive, and receive aggressive intravitreal and systemic antiviral therapy. Even straightforward clinical scenarios such as these can present diagnostic dilemmas, as not all clinical endophthalmitis are confirmed to be infectious even with molecular techniques² and other infections can mimic ARN.³ Neoplastic conditions can also mimic intraocular infections (Supplementary Figure 1).

University of Miami Miller School of Medicine, Bascom Palmer Eye Institute, Miami, FL, USA

Correspondence: JL Davis, University of Miami Miller School of Medicine, Bascom Palmer Eye Institute, 900 NW 17th street, Miami, FL 33136, USA
 Tel: +1 305 326 6377;
 Fax: +1 305 326 6071.
 E-mail: jdavis@med.miami.edu

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Most posterior uveitis presents at least some difficulties in clinical diagnosis, in part because of variation introduced by the host response. Ipsilateral choroiditis in immunocompetent patients ('thumbprint lesions') following herpes zoster ophthalmicus (Supplementary Figure 2) does not progress to ARN, but is clearly related to the prior infection, perhaps as an immunologic host response.⁴ Serpiginous choroidopathy is classified as a non-infectious uveitis, but there is a strong epidemiologic association with tuberculous infection and a serpiginous-like choroidopathy,^{5,6} which could represent either direct choroidal infection or a hypersensitivity reaction to infection elsewhere. It has a different pattern of disease than classic serpiginous choroidopathy⁷ or the classic choroidal granulomas and dense periphlebitis that are pathognomonic for tuberculous uveitis (Supplementary Figure 3). The apparent requirement for both antituberculous treatment and corticosteroids in serpiginous-like choroidopathy as well as other cases of tuberculous uveitis supports a strong host-pathogen component in the clinical disease.⁸

Although some forms of uveitis, such as birdshot or sympathetic ophthalmia, are undoubtedly autoimmune, others, such as pars planitis and sarcoidosis, which are now classified as non-infectious, may ultimately be shown to be either direct infection or host response to infection.⁹ Multifocal choroiditis (MFC) and presumed ocular histoplasmosis syndrome (POHS) are distinguishable by subtle clinical appearance,¹⁰ but most reliably by the presence of vitreitis, which by definition is absent in POHS. If vitreitis is absent in MFC it is unlikely there is active choroidal inflammation requiring treatment.¹¹ It is not clear whether it is reasonable to consider POHS an infectious choroiditis (or the sequela of one), but not MFC, when they are so similar in appearance and MFC is more likely to have active inflammation. Whether the chorioretinal lesions of POHS harbor organisms has not been proven. In immunocompromised individuals histoplasmosis produces an endophthalmitis with retinal involvement rather than a choroidal abscess.^{12,13} Transient posterior uveitis such as acute posterior placoid pigment epitheliopathy or multiple evanescent white dot syndrome are also candidates for infections or at least the aftermath of a self-remitting infection.^{14,15} The boundaries between non-infectious and infectious uveitis are thus somewhat blurred.

Most definite intraocular infections involve the vitreous cavity (endophthalmitis), in the case of extracellular organisms, or the retina (chorioretinitis), in the case of intracellular organisms such as viruses and protozoa. Different clinical appearances occur with different organisms. Candidal endophthalmitis is more likely to be located in the retina or vitreous than

aspergillus endophthalmitis, which preferentially grows in the subretinal and sub-retinal pigment epithelial (RPE) spaces and viral invades vessels in the choroid.¹⁶ Other organisms, such as nocardia, also grow preferentially at the RPE level.¹⁷ It is possible that factors other than anatomy, such as oxygen levels or cell type influence the locus of initial infection. A limited spectrum of organisms cause choroidal abscess, possibly because of the redundant circulation.¹⁸ The initial focus of infection may be obscured by subsequent spread of the destructive process, for example, from retina to choroid in toxoplasmosis.¹⁹ Bacterial infections often progress rapidly so that the initial point of infection cannot be detected, but localized infections are recognized (Supplementary Figure 4). Screening for fungal endophthalmitis in hospitalized patients with fungemia was once widely performed. With the advent of effective preemptive treatment, most retinal lesions found on screening are actually microangiopathy rather than true infection.²⁰

Diagnostic dilemmas for endophthalmitis arise when any of the key signs are missing, such as pain, redness, hypopyon, fibrin, or the vitreous is relatively clear. In chorioretinitis, problems in diagnosis mainly arise when preretinal opacities prevent adequate examination of the retina-choroid, or the pattern of infection is atypical for that expected, for example, when necrotizing herpetic retinitis is focal rather than diffuse (Supplementary Figure 5). The patient's history may lack clues to the source of a blood-borne infection causing an endogenous endophthalmitis. Similarly, immune-system impairment or residence in an endemic area for toxoplasmosis that could explain a susceptibility to an infectious chorioretinitis may be absent. Nonetheless, a comprehensive history in addition to physical examination of the eye remains an important first step in diagnosing infectious uveitis.

Key ocular signs in endophthalmitis

Hypopyon is the classic diagnostic sign of endophthalmitis, yet is unreliable as a sole indicator. Flat-topped, layered, and shifting hypopyons are common in Behcet uveitis. They can also be manifestations of leukemic infiltration or diffuse retinoblastoma, and unfortunately for the clinician can be seen in very early and rapidly progressive infectious endophthalmitis in which sufficient fibrin has not formed to mold the upper edge of the hypopyon. Drug reactions, such as 'sterile endophthalmitis' from intravitreal injection of triamcinolone acetonide or from oral administration of rifabutin also produce non-infectious hypopyon (Supplementary Figure 6).²¹ Except for Behcet, the hypopyon of non-infectious uveitis is more likely to have a curved upper border (like a fingernail or 'onyx'). The

eventual appearance of a hypopyon after waxing and waning postoperative inflammation with partial response to topical corticosteroids is almost always an indication to proceed with culture and intravitreal antibiotic treatment.

Key ocular signs in chorioretinitis

For chorioretinitis, the relevant clinical signs include presence or absence of necrosis of the retina; size, shape, and orientation of the lesions; degree of opacity; apparent thickness; and the confluency or focality of the lesions, along with their color and border characteristics. Associated inflammatory signs such as arteriolar or venular sheathing, vascular occlusion, frosted branch angiitis, (Supplementary Figure 7) and the intensity of vitreous and anterior chamber inflammation are also important. Pattern recognition is vastly assisted by experience because of the number of characteristics that must be recognized and the wide variation.

Syphilitic uveitis can mimic both endogenous endophthalmitis, with hypopyon and dense vitreous opacities, and viral chorioretinitis with retinal swelling and preretinal opacities (Supplementary Figure 8).²² After resolution, mild pigmentary changes can be seen with damage to the retinal pigment epithelium, but syphilis is rarely necrotizing.²² Conversion to a necrotizing chorioretinitis has been described after intravitreal injection of triamcinolone.²³

Table 1 summarizes the clinical features of the most common types of chorioretinitis and their variants. Figure 1 depicts diffuse toxoplasmosis, the infection which is most commonly confused with acute retinal necrosis, leading to delays in treatment.

Ancillary testing to confirm the working diagnosis

It is assumed that all patients with intraocular inflammation will have relevant histories performed, radiographs, and basic blood laboratory testing,

Table 1 Key clinical features distinguishing different etiologies of infectious chorioretinitis

	<i>Location</i>	<i>Confluence</i>	<i>Border</i>	<i>Thickness</i>	<i>Vasculitis</i>
Acute retinal necrosis ²⁴	Peripheral Multifocal or posterior ²⁵	Confluent, Rapid centripetal spread	Smooth with large satellites	Necrotizing Full thickness, opaque, edematous	Occlusion in and outside lesions
Cytomegalovirus	Random Vasocentric	Unifocal or multifocal, Central healing, usually concentric spread	Granular small satellites	Necrotizing, Superficial	Occlusion in lesions FBA reported ²⁶
Syphilis	Random Posterior polar predominance	Diffuse	Poorly defined	Non-necrotizing, Translucent, edematous	Vascular leakage Venous occlusion ²²
Toxoplasmosis, focal	Random	Unifocal with border healing	Smooth	Thick, inner retina or full thickness	Arteriolar > venular sheathing, FBA reported
Toxoplasmosis, diffuse ^{27,28}	Random	Confluent, random spread	Smooth	Usually thick	Arteriolar > venular sheathing

FBA, frosted branch angiitis: heavy deposits of inflammatory material along multiple arteriolar and venular branches.

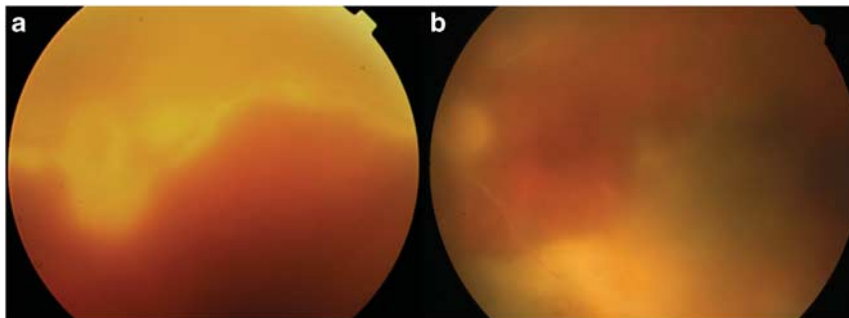


Figure 1 Diffuse toxoplasmosis. The chorioretinitis was initially misdiagnosed as acute retinal necrosis. (a) This elderly man may have acquired toxoplasmosis while he gardened at his new home; he was IgM and IgG antibody positive for toxoplasmosis. Note the focal lesion on the left that appears to have spread diffusely into a smooth-bordered chorioretinitis. There is vitreous haze. PCR from the vitreous was positive for toxoplasmosis. (b) This elderly woman developed what appeared to be a classic focal reactivation of toxoplasmic chorioretinitis after cataract extraction. She was treated with multiple courses of doxycycline, recurring each time the medication was stopped. The infection spread inferiorly and temporally. Vision was hand motions only.

including syphilis serology. Chorioretinitis is almost always an indication for HIV testing.

A complete blood count, chemistry panel, urinalysis, C-reactive protein, herpes simplex, cytomegalovirus, Epstein-Barr virus, and toxoplasmosis infectious serologies can help assess prior exposures even if they do not directly confirm the etiology of the intraocular infection. Prior chickenpox infection is usually accepted in lieu of varicella zoster serology; prior varicella vaccination does not necessarily rule out varicella-related acute retinal necrosis.

Angiography is most useful in toxoplasmic chorioretinitis, which has a distinctive early blockage in the lesion with a late hyperfluorescent border with fluorescein dye. On indocyanine green angiography, distinctive dark dots surround the lesion (Figure 2). Optical coherence tomography (OCT) also typically shows inner retinal hyperreflectivity. In thick, elevated, opaque lesions, OCT is very useful in ruling out choroidal or subretinal involvement.

Ultrasonography is routinely used in the diagnosis of endophthalmitis when the posterior segment cannot be viewed. If the vitreous is not involved, it is less likely to be endophthalmitis unless there is limited exogenous endophthalmitis with an anterior entry or keratitis. Ultrasound is nonspecific, however: it can only indicate severity of the posterior involvement and whether retinal detachment or abscess is present. Vitreitis may be

minimal in intracapsular, delayed endophthalmitis, leading to misdiagnosis, however, vitreitis is ordinarily the *sine qua non* of endophthalmitis (Figure 3). Features compatible with endophthalmitis include strands and membranes with reduced mobility. For delayed postoperative infection, the extent of intracapsular infection determines the amount of surgical debridement that will be required including whether the intraocular lens needs to be removed. Ultrasound can be used to predict findings before surgery. In persistent endophthalmitis, ultrasound may help locate infected foci (Figure 4).

PCR testing of vitreous specimens in suspected bacterial or fungal endophthalmitis is well established in certain centers.^{2,29-34} Concordance with culture is close to 100%, with greater sensitivity with PCR testing.^{29,34} The presumption is that PCR will eventually replace culture and sensitivity testing (by amplifying loci known to determine resistance to antibiotics³⁵) and enable the detection of unsuspected, fastidious, or previously unknown pathogens.^{9,36,37} Intraocular Whipple disease is diagnosable by PCR of aqueous humor or vitreous. Two positive results are considered a definitive diagnosis of uveitis related to Whipple disease.³⁸

There are multiple case series summarizing the results of PCR testing of aqueous or vitreous humor in cases in which culture is inefficient or unavailable, mainly in the case of viral or protozoal chorioretinitis.³⁹⁻⁴³ Aqueous

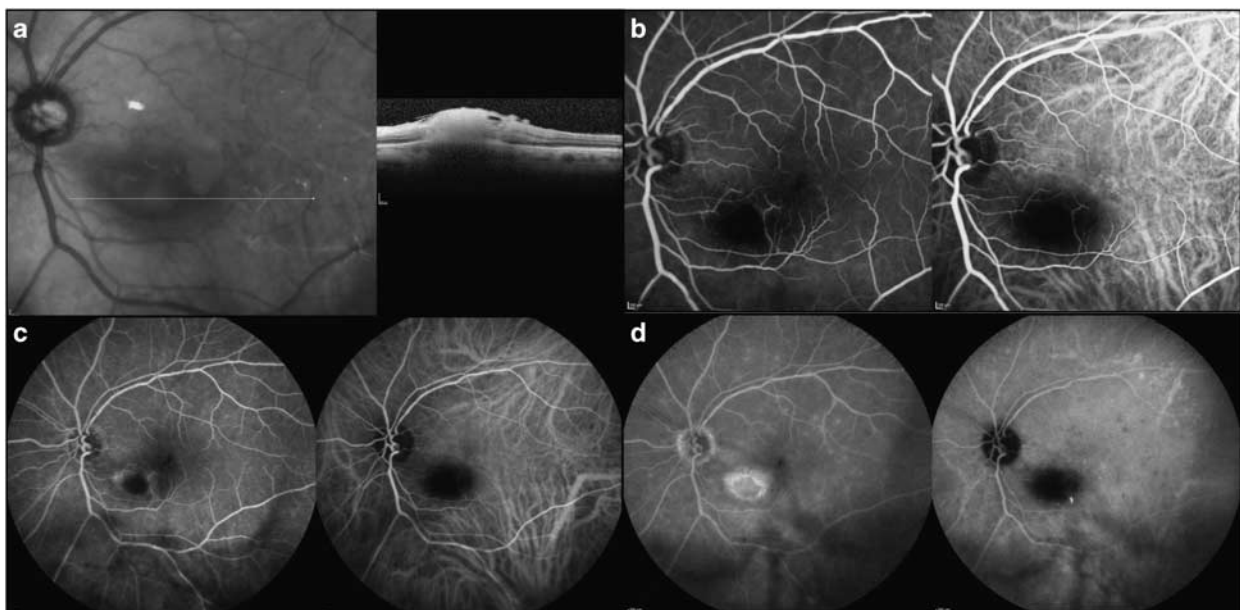


Figure 2 Imaging studies of toxoplasmic focal chorioretinitis. (a) OCT image through lesion showing inner retinal hyperreflectivity with shadowing of the outer retina and choroid. (b) Early angiogram, 50 s. There is hypofluorescence of the lesion in both the fluorescein (left) and the indocyanine angiogram (right). (c) Mid-phase of the angiogram, 2.33 min. Hyperfluorescence begins at the edge of the focal lesion. The ICG remains hypofluorescent. (d) Late angiogram, 15.11 min. The lesion is almost fully stained with fluorescein. In the ICG the lesion is hypofluorescent and surrounded by dark dots most visible in the temporal macula.

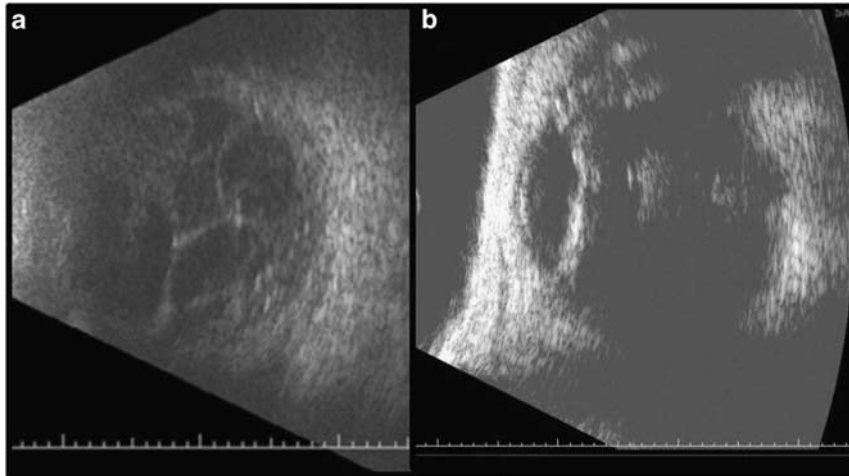


Figure 3 Ultrasonography in the diagnosis of postoperative endophthalmitis. (a) Classic appearance of vitreous stands and membranes on B-scan ultrasound. Variations in gain can alter the appearance of the vitreous opacities. (b) Capsular hyperreflectivity in a case of delayed onset endophthalmitis with dense intracapsular deposits. The vitreous contains some dense deposits but is not diffusely infiltrated. Absence of vitreous inflammation or opacities is suggestive that endophthalmitis is not present, except for limited anterior forms.

humor appears to be an adequate substrate for testing and vitreous tap is rarely needed although vitreous humor can also be used for testing. Culture of vitreous fluid for toxoplasmosis using viral media has been reported to be possible in cases of extensive, diffuse infections.⁴⁴ Tuberculous chorioretinitis⁴⁵ is potentially confirmable by PCR testing, although higher copy numbers seem to be required than exist in ocular specimens that have not been grown out in culture.⁴⁶ PCR protocols optimized for the confirmation of *Mycobacterium tuberculosis* from cultures rather than from biologic fluids are not efficient diagnostic tools and yield false negatives when applied to ocular specimens. Intraocular syphilis antibody can be assayed from aqueous humor and PCR confirmation of syphilitic uveitis has also been reported.⁴⁷

Table 2 summarizes the preferred diagnostic tests that can be performed on intraocular fluid. Culture of other body fluids can be helpful in endogenous uveitis and serology is helpful in syphilis. Delayed-type hypersensitivity reactions (Mantoux) and interferon- γ release assays are helpful in the diagnosis of tuberculous chorioretinitis.

In some cases, retinal biopsy or aspiration is the next step after PCR or culture. Usually this is in cases in which lymphoma is in the differential, which would require histopathology for diagnosis. Retinal biopsy showing cytomegalic inclusions or toxoplasmic tachzoites can be diagnostic. Confirmation by immunohistochemical testing is advised in herpes simplex or varicella zoster. Histopathology has distinct advantages over selective molecular tests such as PCR when the clinical condition is a true unknown and testing is not just for confirmation.

It enables a correct assignment of the case to non-infectious uveitis, infectious uveitis, or neoplasia. The slides acquired can be stained with iodine-containing preparations to identify organisms that would be Gram positive on conventional smears, stained with selective antibodies, or processed by *in situ* hybridization as a slide-based form of PCR.⁴⁸

Response to empiric therapy as a diagnostic maneuver

The first goal in empiric therapy in suspected infectious uveitis is to reduce the risk of vision loss by treating potentially rapidly progressive and destructive infections before confirmatory testing is complete. The comparable success of vitreous tap and injection of antibiotics *vs* pars plana vitrectomy with injection of antibiotics may relate in part to the rapidity with which the antibiotics can be administered with the tap and inject protocol.⁴⁹ It is possible that immediate tap for PCR with intravitreal antibiotics followed by pars plana vitrectomy when operating room time can be arranged would lead to better visual outcomes by removing inflammatory mediators and lytic enzymes from the eye.

For chorioretinitis, it is common to begin antiherpetic therapy at the time of presentation if acute retinal necrosis is suspected. A diagnostic aqueous tap for herpes simplex, herpes zoster, and cytomegalovirus can be stored until results of syphilis serology are known and then can be used to specify preferred antiviral (valganciclovir *vs* valacyclovir) and in the case of herpes simplex or zoster, the dose, as zoster usually requires higher antiviral doses.

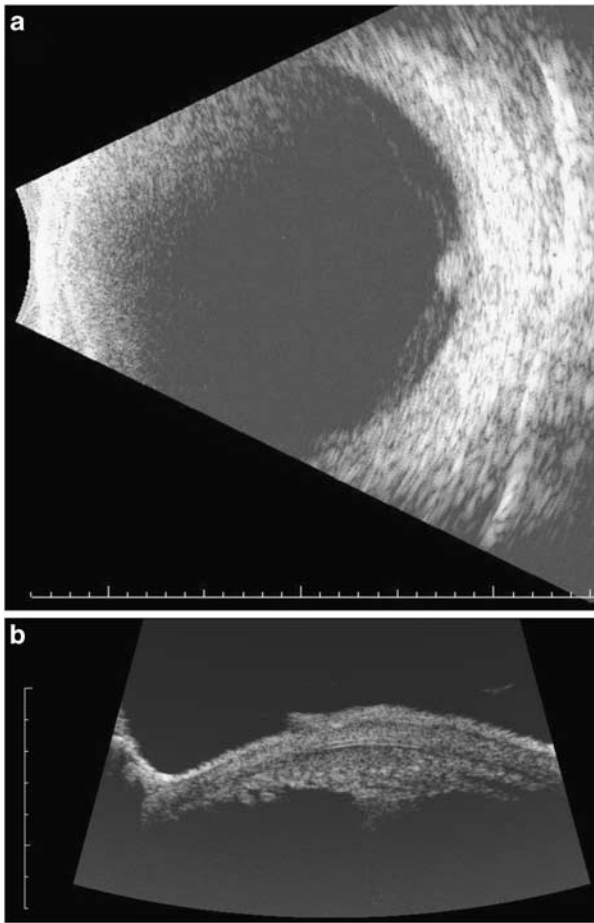


Figure 4 Persistent fungal endophthalmitis following pars plana vitrectomy and removal of infected capsular bag. During a second surgery the entire bag and lens implant were removed, but inflammation persisted. Ultrasound confirmed focal deposits in the ciliary body region in the meridian where the infected capsular plaques had been noted. (a) Anterior to the equator at 3:00 (3EA) there is a focal deposit in the ciliary body region. (b) Anterior segment B scan confirms a ciliary body deposit at the 3:00 position (3T). Notice the ciliary processes to the left of the deposit. At surgery, a focal white deposit was found between 3 and 4:00 adherent to the ciliary processes. Removal of it with the vitreous cutter and picks followed by repeated injections of amphotericin enabled the infection to be cured.

The potential damage from high-dose empiric corticosteroids is extreme in undiagnosed infectious uveitis. Oral corticosteroids or intravenous corticosteroids are preferred to regional corticosteroids because they are more easily reversible. Nonetheless, corticosteroid administration without specific antimicrobial coverage can lead to vastly worsened prognosis. It is usually more helpful to try to elicit a response with specific anti-infective treatment first and then use corticosteroids as an adjunct to protect the eye against the secondary inflammatory reaction in infections. In endophthalmitis, it has been difficult to demonstrate that routine injection of intravitreal corticosteroids is beneficial.^{50,51} They are avoided in fungal endophthalmitis, viral chorioretinitis in immunocompromised patients, and syphilitic uveitis except for topical agents, however, in diagnostic dilemmas a point is often reached at which a patient's failure to respond to empiric anti-infective treatment and negative diagnostic tests culminates in an aggressive therapeutic trial of corticosteroids for a presumption of autoimmune posterior or panuveitis. Establishing a timeframe at the initiation of empiric treatment in which a response is expected is helpful in interpreting results. In general, effective treatment for viral retinitis should lead to no progression after treatment with full healing within 4 to 6 weeks, bacterial infections should improve within 72 h, syphilis should improve within 1 week, and tuberculosis should improve within 3 to 6 weeks.

Summary

Ocular infections rare enough and variable enough that the first clinical impressions are often incorrect. Focused clinical skills and broad experience are helpful. Knowledgeable use of ancillary testing is essential. Treatment is urgent in some infections, especially acute endophthalmitis and acute retinal necrosis. The safe use of corticosteroids in equivocal cases and masquerades requires mastery.

Table 2 Preferred diagnostic testing of intraocular fluid in infectious posterior uveitis

Infectious uveitis	Culture	PCR	Antibodies
Viral—CMV	No	Yes, untreated	Yes, treated or healed
Viral—ARN, herpes simplex and herpes zoster	No	Yes, untreated	Yes, treated or healed
Bacterial	Yes	Available in some centers	No
Fungal	Yes	Available in some centers	No
Protozoal—focal toxoplasmosis	No	Large lesions or immunocompromised hosts	Yes
Protozoal—diffuse toxoplasmosis >1 clock hour in extent	Possible, not used routinely	Yes	Yes
Spirochetes	No	Available in some centers	Yes
Tuberculosis	Yes, with confirmatory PCR	Requires high copy numbers in biological specimens	No

Conflict of interest

The author declares no conflict of interest.

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