Clinical Infectious Diseases

STATE-OF-THE-ART REVIEW

State-of-the-Art Review: Ocular Infections

Miriam B. Barshak,[1,2] Marlene L. Durand,[1,2,3] Akash Gupta,[1,4] Amir M. Mohareb,[1,2] Thomas H. Dohlman,[3] and George N. Papaliodis[2,3]

[1]Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts, USA; [2]Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA; [3]Department of Ophthalmology, Massachusetts Eye and Ear, Boston, Massachusetts, USA; and [4]Mass General Brigham Medical Group, Haverhill, Massachusetts, USA

Keywords. ocular infection; conjunctivitis; keratitis; uveitis; endophthalmitis.

Eye infections are common and often generate visits to emergency departments, primary care settings, and ophthalmology or other eye care clinicians. Most episodes are managed without infectious disease (ID) specialty input. Infectious disease specialists are often consulted regarding severe or immediately sight-threatening infection, diagnostic uncertainty, antimicrobial resistance, intolerance or failure of standard treatment, or concern for associated extraocular infection or comorbidities. Diagnosing and managing ocular infections can be inherently challenging. For ID specialists, there may be additional challenges in performing the exam and in understanding the anatomy, the ophthalmologist's note, the natural course of these infections, and the medical and interventional treatment options. Here we highlight some common and uncommon ocular infections with a goal of addressing these challenges.

ANATOMY

The sclera and cornea form the outer layers of the eye; the retina forms the innermost layer. Between these is the uvea, a highly vascular and pigmented layer composed of iris, ciliary body, and choroid (Figure 1). The retina is part of the central nervous system and has a blood–eye barrier that resembles the blood–brain barrier, a consideration in choosing antibiotics to penetrate into the eye. The anterior segment (cornea to lens) is filled with aqueous humor, which is continuously produced by the ciliary body and reabsorbed. The gel-like vitreous fills the posterior segment and is not regenerated.

UNDERSTANDING THE OPHTHALMOLOGIST'S NOTE

The ophthalmologist's note first reports visual acuity, intraocular pressure, extraocular muscle movement, and color vision. The best vision is reported: 20/40–1 means the patient made 1 error on the 20/40 line of the Snellen chart. Vision worse than 20/200 ("big E" on Snellen chart) is reported as the best of the following: "count fingers," "hand motion," "light perception," or "no light perception." Tonometry measures intraocular pressure; this may be elevated from glaucoma but also transiently from intraocular inflammation. The note then relays the eye examination from front to back. Table 1 lists common abbreviations.

CONJUNCTIVITIS AND KERATITIS

Vignette

A 73-year-old woman presents with 2 days of left eye watery drainage, redness, pain, and visual changes, and a 5-day history of vesicular rash on the left forehead. On gross examination, there is conjunctival injection; slit lamp examination shows corneal edema with pseudo-dendritic lesions on fluorescein staining (Table 2, Figure 2). She is diagnosed with herpes zoster ophthalmicus (HZO), causing keratoconjunctivitis, and started on oral valacyclovir.

Infectious Conjunctivitis

Acute infectious conjunctivitis (AIC) is the most common type of eye infection [4]. Most cases of conjunctivitis are managed without the input of an ID specialist (Table 3). Viral AIC is more common than bacterial in adults; the reverse is true in children. Adenoviruses cause most viral AIC (up to 90% of cases), while *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most common causes of bacterial AIC.

Infectious Keratitis

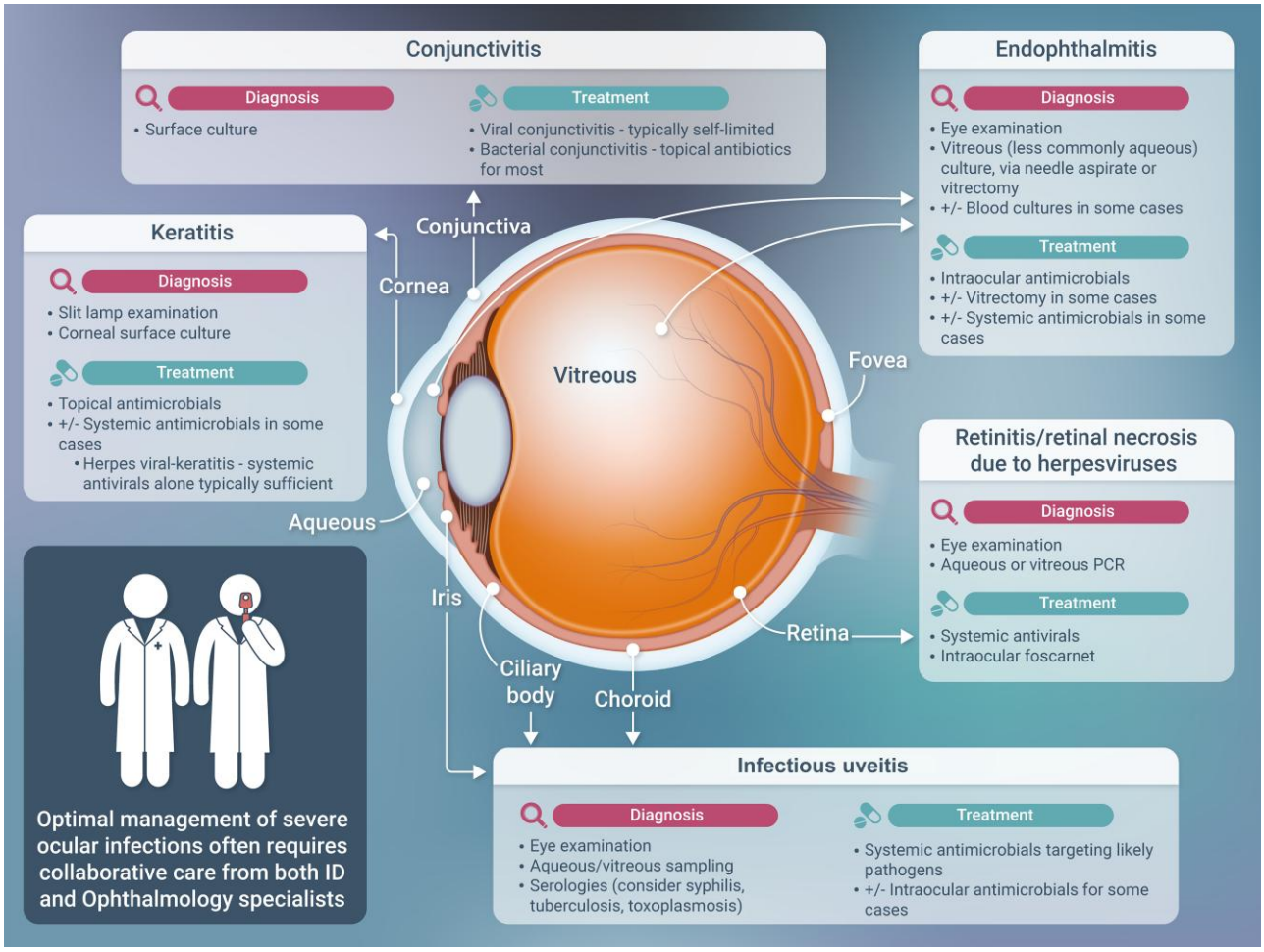
Because the cornea transmits and refracts light, corneal infections can lead to vision loss by causing corneal swelling, scarring, and perforation. Corneal infections caused by bacteria, fungi, and parasites are called "microbial keratitis" or "infectious corneal ulcers." These infections are associated with unilateral eye pain, injection, photophobia, and decreased vision. In the United States, the primary risk factor for microbial keratitis is contact lens use—specifically, lapses in hygiene associated with contact lenses, such as bathing or sleeping in lenses, rinsing in tap water, and reusing lens cases long-term [13]. Other risk

Received 28 April 2024; editorial decision 19 July 2024

Correspondence: M. B. Barshak, Division of Infectious Diseases, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114 (mbarshak@partners.org).

Clinical Infectious Diseases® 2024;79(5):e48–64

https://doi.org/10.1093/cid/ciae433



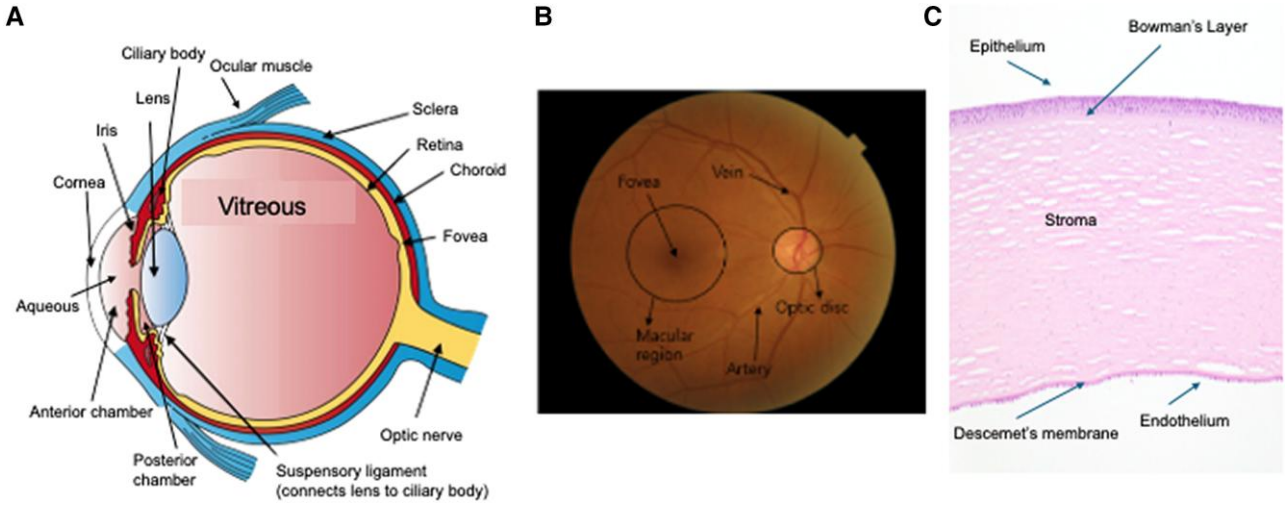


Figure 1. Eye anatomy. *A*, Cross-section of the eye, highlighting structures important for understanding ocular infections: the outer layers of the eye (sclera and cornea), middle layer (uvea, including iris, ciliary body, and choroid), innermost layer (retina), aqueous humor (filling the anterior segment, cornea to lens, produced continuously and reabsorbed), and vitreous humor (filling the posterior segment, gel-like, not regenerated) [1] (https://creativecommons.org/licenses/by/3.0/deed.en). Figure adapted by addition of labels for ciliary body, posterior chamber, and ocular muscle. Most hematogenous eye infections begin by seeding the uvea, which is highly vascular. *B*, Funduscopic view, highlighting the vasculature that may be affected by infection, the macula (responsible for the sharpest vision and central vision, with the fovea at its center), and the optic disc (the head of the optic nerve) [2]. *C*, A light micrograph showing a cross-section of a human cornea. The various layers from anterior (front) to posterior (back) are the epithelium, showing dark-stained cell nuclei; the acellular Bowman's layer; the stroma; Descemet's membrane; and the endothelium. Courtesy of Dr. Anna Stagner.

Table 1. Glossary of Common Ophthalmology Terms and Abbreviations

Abbreviation/Term	Definition
Eyes	
OD (oculus dexter)	Right eye
OS (oculus sinister)	Left eye
Visual Acuity	
BCVA	Best corrected visual acuity
$V_A$cc	Visual acuity with ("c") correction of refractive error (eg, with glasses)
$V_A$sc	Visual acuity without ("s") correction
V_APH	Visual acuity looking through a pinhole, which mimics optimal refraction
20/40-2	Patient reads the 20/40 line on the Snellen chart with 2 errors
CF@2 feet	Patient's best vision is the ability to count the examiner's fingers ("CF") at 2 feet
HM	Patient's best vision is "hand motion" vision (patient can detect examiner moving hand)
LP	"Light perception" (patient can tell when examiner turns on and off a point light source such as a flashlight)
NLP	No light perception
Intraocular pressure	
T	Tonometry, measure of intraocular pressure; normal is 10–20 mmHg
Cornea	
K	Abbreviation for cornea
Kerato	Prefix referring to the cornea (from Latin "cornu" = horn, "kerato" prefix from Greek for horn or cornea)
PK	Penetrating keratoplasty, full-thickness corneal transplant
KP	Keratic precipitates, clusters of white blood cells from the aqueous that have adhered to the endothelial surface of the cornea
Fine KPs	Small KPs, also called "granular" KPs
Granulomatous KPs	Large KPs, also called "mutton fat KPs," as if liquid fat was thrown against a window. There are no histologic granulomas in these KPs, but the term refers to the fact that this type of KP is common in tuberculosis, sarcoidosis, and other granulomatous conditions. Of note, corticosteroid eyedrops can transform granulomatous KPs to fine KPs
Anterior chamber	
AC	Anterior chamber, area between iris and cornea
"cells"	White blood cells, rated on a 0–4 scale (0 is normal)
"flare"	Protein that is visible as haziness in the aqueous (0–4 scale, 0 is normal)
Iris	
Synechiae	Adhesions, usually between the iris and cornea or iris and lens
Lens	
NS	Nuclear sclerosis, a common type of cataract (opacification of lens)
PC IOL	Posterior chamber intraocular lens, the artificial lens placed during cataract surgery (placed in posterior chamber of eye)
Vitreous	
"cells"	White blood cells, rated on a 0–4 scale (0 is normal)
"string of pearls"	Description of vitreous infiltrates that can suggest a fungal etiology in endophthalmitis cases
Vitrectomy	Surgical procedure in which the gel-like vitreous is removed with an instrument (vitrector) that has a piston-like cutting action (see Figure 4*E*)
PPV	Pars plana vitrectomy—the vitrectomy is always performed through the pars plana portion of the ciliary body, which is avascular
Retina	
C/D	Cup to disc ratio of optic nerve; normal is 0.4
Vascular "sheathing"	Inflammation around blood vessels
Vessels with "candle wax drippings"	Typical of granulomatous infections such as tuberculosis or sarcoidosis
Macula	Provides central and sharpest vision, color vision
Peripheral retina	Area outside of the macula, provides low-light and peripheral vision
Diagnostic tools	
B scan	"Brightness" scan-ultrasound of the eye, can detect retinal detachment, inflammation in the vitreous, and other pathology
FA	Fluorescein angiogram, best test for retinal vessels, also has implications for choroidal circulation and structures in choroid and retina; can detect vessel leakage, eg, from diabetic retinopathy or vasculitis
ICG	Indocyanine green angiography—used for imaging choroidal circulation
OCT	Optical coherence tomography—noninvasive test that provides a "cross-section" view of the retina and optic nerve head
AS-OCT	Anterior segment OCT, provides a "cross-section" view of the cornea and anterior segment structures

factors for microbial keratitis include eye trauma and ocular surface disease (eg, exposure keratopathy from Bell's palsy). A recent outbreak of carbapenemase-producing *Pseudomonas* was linked to artificial tears manufactured in India [14].

On a penlight exam, microbial keratitis is associated with conjunctival injection. A white opacity may be seen in the cornea (Figure 3). A slit lamp exam allows evaluation of the extent of keratitis and any intraocular inflammation, which may include

Table 2. Example of an Ophthalmologist's Note for the Left Eye Examination of a 73-Year-Old Woman With Herpes Zoster Ophthalmicus, Presenting With a Painful Vesicular Rash on her Left Forehead and Eyelids and a Red Left Eye

	Examination Feature	Result	Interpretation
Initial exam: slit lamp	$V_A$cc	20/20-3	"$V_A$cc" = visual acuity with correction; ie, correction of refractive error (eg, via glasses); "20/20-3" = reads 20/20 line on Snellen chart with 3 errors
	T	22	T = tonometry, measurement of intraocular pressure; normal is 10–20 mmHg so hers is slightly elevated
	Pupils	PERRLA	Pupils equal, round, and reactive to light and accommodation
	EOMs	Full	Extraocular muscle movements (EOMs) are normal
	Lids/lashes	Edema, erythema, crusted vesicles at margins	Left eyelid findings as noted
	Conjunctiva	3+ Injection, diffuse chemosis	Injection = conjunctival redness (hyperemia from dilated blood vessels), chemosis = conjunctival edema
	K	Nasal cluster of pseudo-dendrites in the epithelium	K = cornea; the findings refer to dendritic (branch-like) appearance of infiltrate in the corneal epithelium, the 6-cell-thick surface of the cornea; this is typical of herpes zoster and herpes simplex (Figure 2)
	AC	Normal, D&Q	AC = anterior chamber is normal, "D&Q" = deep and quiet (not shallow in depth, and no inflammation)
	Iris	Normal	Normal iris
	Lens	1+ NS	NS = nuclear sclerosis, a common type of cataract (lens opacification); 1+ means slight on a qualitative 0 to 4+ scale
	Vitreous	Normal	Normal vitreous (no inflammation)
Follow-up exam, after 2 wk of valacyclovir treatment for herpes zoster ophthalmicus (HZO), at which time the skin lesions have crusted over and resolved	…	…	…
Fundus exam	Disc	Normal	Disc = optic disc
	C/D ratio	0.4	Cup to disc (C/D) ratio is 0.4, which is normal
	Macula	Normal	The macula provides the sharpest vision and is normal here
	Vessels	Normal, no vascular sheathing	The absence of vascular sheathing is specified because the author of the note wants to emphasize that viral involvement of the retina is absent (early involvement may be seen by a retinal vasculitis)
	Periphery	Normal	Peripheral retina (ie part of retina outside of the macula) is normal
Slit lamp	$V_A$cc	20/80	$V_A$cc = vision with correction (eg, glasses) is only 20/80 now, but better with pinhole correction
	V_APH	20/30-1	V_APH = vision looking through a pinhole (PH)—this mimics optimal refraction and hers improved to 20/30 with 1 error
	T	19	Intraocular pressure is now normal at 19 (normal 10–20)
	Lids/lashes	Normal	The prior rash on the eyelids has resolved
	Conjunctiva	Trace injection	Trace conjunctival hyperemia (redness), much improved from prior exam
	K	Multiple patches of stromal haze; fine KPs	Cornea (K) has hazy infiltrate in stroma (central layer of cornea). KPs are keratic precipitates = white blood cells on endothelial surface of cornea. "fine" means these KPs are small
	AC	1+ cell, 2+ flare	AC = anterior chamber, "1+ cell" = white blood cells in aqueous, only 1+ on scale of 0 to 4+ (normal is 0). "Flare" is protein that has leaked into the aqueous with inflammation, the amount graded on a 0 to 4+ scale
	Iris	Normal	The combination of inflammation in the AC plus the stromal keratitis (corneal inflammation) gives a diagnosis of keratouveitis
	Lens	1+ NS	Same 1+ cataract as before
	Vitreous	Normal, no cells	No white blood cells; ie, the inflammation is confined to the anterior segment of the eye
			Comment: The exam shows that there is now an anterior uveitis; topical corticosteroids will be added while continuing the oral valacyclovir. The fundus exam is normal

a hypopyon that is typically sterile in keratitis. The microbial diagnosis is usually made via surface culture, obtained by an ophthalmologist from corneal scrapings. Most cases in the United States are bacterial, involving organisms such as *Pseudomonas*, *Staphylococcus aureus*, and streptococcal species, but other organisms, including fungi and *Acanthamoeba* (associated with tap water and contact lens cases), must also be considered. Fungal infections are much more common in developing countries, often with ocular surface trauma. *Acanthamoeba* and fungi have a particularly poor prognosis, but other organisms can also cause severe corneal destruction [15].

Viral keratitis is most commonly due to herpes simplex virus (HSV) and varicella zoster virus (VZV). Varicella zoster virus keratitis typically develops within 1 month of onset of HZO. Patients with HZO should be referred to an ophthalmologist, urgently if there are ocular signs or symptoms. For both viruses, the slit lamp exam classically shows a branching, dendritic, or pseudo-dendritic pattern of epithelial changes and/or ulceration

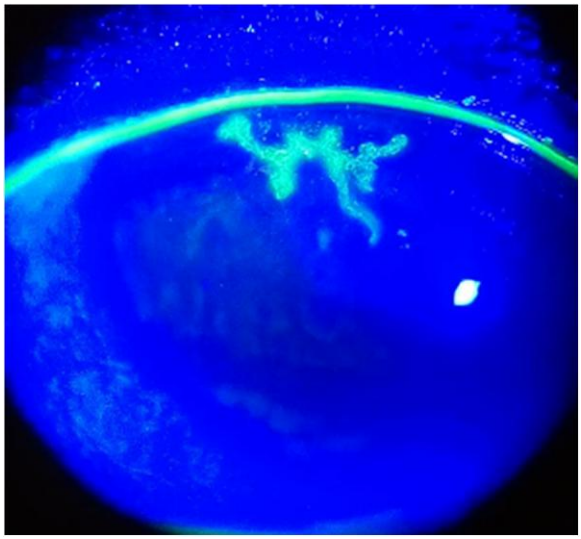


Figure 2. Herpetic keratitis. In corneal infections with HSV or VZV keratitis, the slit lamp exam may show a "dendritic," "pseudo-dendritic," or "geographic" branching pattern of epithelial changes and/or ulceration or infiltrate in the corneal stroma [3] (https://creativecommons.org/licenses/by-sa/4.0/deed.en; no changes were made). Abbreviations: HSV, herpes simplex virus; VZV, varicella zoster virus.

(Figure 2). Treatment consists of antivirals (Table 3). Corneal scarring and anesthesia can complicate VZV keratitis in up to 60% of cases, making the cornea more susceptible to subsequent ulceration, bacterial superinfections, and perforation. Vaccination is over 90% effective at preventing VZV infections [16].

Microbial keratitis is treated with frequent topical antibiotic drops (Table 3). Systemic therapy may be added in some cases. Severe microbial keratitis may require adjunctive treatments to promote epithelial healing and seal small perforations, including photodynamic therapy, phototherapy, cryotherapy, collagen crosslinking, tissue adhesives, tarsorrhaphy, amniotic membrane transplantation, conjunctival flaps, and scleral or rigid gas permeable contact lenses. In rare cases, surgical excision of the infected tissue and placement of a temporizing corneal transplant is required for source control, with a subsequent definitive corneal transplant once infection is eradicated. The survival of grafts placed during acute keratitis is poor, in part because local immune suppression must be minimized in order to control infection, which increases the risk of graft rejection and failure [17, 18]. Some patients experience repeated graft failure, and a keratoprosthesis (artificial cornea) is the only option to address corneal blindness. The most successful and commonly used type of keratoprosthesis is the Boston keratoprosthesis (Figure 3) [19].

ENDOPHTHALMITIS

Vignette

A 24-year-old woman with history of injection drug use (IDU) presents with pain and deteriorating right eye (oculus dexter [OD]) vision over the prior month, without fevers, sweats, or other systemic symptoms. Visual acuity is 20/400 OD (20/20 oculus sinister [OS]). Funduscopic examination reveals a white lesion in the vitreous. She is diagnosed with endogenous endophthalmitis, likely fungal. Intravitreal injections of vancomycin, ceftazidime, and voriconazole are given, and blood cultures are drawn. She is admitted and started on systemic high-dose fluconazole. The vitreous aspirate culture and blood cultures are negative. By day 3, the vitritis has worsened. A vitrectomy (surgical debridement of the vitreous) is performed; vitreous cultures grow a fluconazole-resistant *Candida* species.

Endophthalmitis means intraocular infection, but, in general use, the term means bacterial or fungal infection of the vitreous and/or aqueous. Endophthalmitis may be exogenous (pathogens introduced via the ocular surface) or endogenous (secondary to bacteremia or fungemia).

Typical symptoms of endophthalmitis include eye pain and decreased vision, although pain may be absent in subacute cases of endophthalmitis (eg, some fungal cases). Fever and systemic symptoms are absent in exogenous endophthalmitis unless the infection has spread to the orbit (panophthalmitis), but systemic symptoms may accompany endogenous endophthalmitis. The eye examination often reveals a hypopyon (Figure 4*A*), which is not sterile in endophthalmitis. Intraocular inflammation may be severe, obscuring the view of the retina. Bacterial infection tends to be acute (1 to several days) and cause diffuse intraocular inflammation. Fungal endophthalmitis is usually more indolent (eg, several days to several weeks), and vitreous inflammation is usually more "clumped" (eg, vitreous "fluff balls") (Figure 4*B*–*D*). A hypopyon may be absent in fungal endophthalmitis.

The diagnosis of endophthalmitis may be confirmed by sampling the vitreous, via either needle aspirate or vitrectomy (Figure 4*E*). In cases of endogenous endophthalmitis with positive blood cultures at the time of presentation, intraocular sampling is usually unnecessary.

Exogenous endophthalmitis is more common than endogenous endophthalmitis and is usually treated by a retina specialist alone. Cataract surgery and intravitreal injections of medications (eg, to treat neovascular macular degeneration) are the most common risk factors for exogenous endophthalmitis in the United States, and gram-positive cocci (especially coagulase-negative staphylococci) are the major pathogens. Eye trauma is the most common risk factor in some countries; coagulase-negative staphylococci and *Bacillus cereus* are common pathogens in posttraumatic endophthalmitis. *Bacillus cereus* causes a fulminant eye infection with rapid visual loss. Prophylactic systemic antibiotics (eg, intravenous vancomycin plus ceftazidime) for 48 hours following penetrating eye trauma have been associated with a greatly reduced incidence of posttraumatic endophthalmitis compared with historic controls (eg, from 10% to 0.9%) [21].

Table 3. Clinical Syndromes, Causative Pathogens, and Treatment Strategies for Infections Causing Conjunctivitis/Keratitis (Medication Doses Assume Normal Renal Function)

Syndromes	Pathogens	Exam Features	Diagnostic Tests	Treatment
Bacterial conjunctivitis	*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Moraxella catarrhalis* are common; less common causes include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Neisseria meningitis*	Purulent drainage, bilateral mattering of the lashes; *Neisseria gonorrhoeae* often causes a hyperacute syndrome with an abrupt onset of copious purulent drainage, eyelid swelling, eye tenderness, preauricular lymphadenopathy, and decreased vision; *Chlamydia trachomatis* (D-K serotypes) conjunctivitis is typically unilateral and subacute, with mucopurulent drainage that persists over weeks to months, a tender preauricular lymph node, and follicles on everted eyelid exam; *Chlamydia trachomatis* (A-C serotypes) causes trachoma	Culture	Topical antibiotics such as trimethoprim-polymyxin or quinolones for most cases not suspected to be from trachoma or sexually transmitted infections; IM ceftriaxone for *Neisseria gonorrhoeae*; oral doxycycline for *Chlamydia trachomatis* types D-K [5]; tetracycline eye ointment and/or oral azithromycin for trachoma; systemic treatment for *N. meningitis* to decrease risk of associated systemic infection [6].
Viral conjunctivitis	Adenoviruses (65%–90% of cases); other causes include herpesviruses, enterovirus, measles, mumps, rubella, SARS-CoV-2, Ebola, Mpox, *Molluscum contagiosum*	Watery drainage is common, but the combination of concomitant pharyngitis, preauricular lymphadenopathy, and contact with another person with a red eye has better positive predictive value for acute viral rather than bacterial conjunctivitis [7]	Viral culture/PCR/antigen testing, as available	Treatment of adenovirus conjunctivitis is supportive;see "keratitis" for HSV/VZV treatment; SARS-CoV-2 treatment decisions are determined by the extraocular syndrome; Mpox treatment may include tecovirimat [8]; *Molluscum* lesions may require excision, cryotherapy, cauterization, or topical agents.
Bacterial keratitis	*Pseudomonas*, *Staphylococcus aureus*, and streptococcal species are common	Conjunctival injection, white corneal opacity (slit lamp exam also shows surface ulceration and depth of infiltrate); may have hypopyon	Culture	Topical therapies, often given hourly at first and then tapered as infection improves: empiric quinolone drops, or vancomycin plus tobramycin drops, then treatment is tailored to culture results. Systemic therapy is added on rare occasions (eg, severe *Pseudomonas* keratitis with extension to sclera). For microbial keratitis (especially for large or vision-threatening ulcers), concentrated topical ("fortified") antibiotics, given frequently (eg, hourly, around the clock) may be required to rapidly control the infection and minimize tissue damage. These antibiotics may require compounding.
Fungal keratitis	Fungi (*Fusarium, Aspergillus,* others)	Conjunctival injection, white corneal opacity (slit lamp exam often shows that infiltrates have fuzzy borders and satellite lesions); may have hypopyon	Culture	Empiric topical natamycin for fungal infection (alternatives: topical amphotericin or voriconazole); systemic therapy (usually oral voriconazole) may be added in some cases. For microbial keratitis (especially for large or vision-threatening ulcers), concentrated topical ("fortified") antibiotics, given frequently (eg, hourly, around the clock) may be required to rapidly control the infection and minimize tissue damage. These antibiotics may require compounding.
Acanthamoeba keratitis	*Acanthamoeba*	White corneal infiltrate; slit lamp exam shows either infiltrate along a corneal nerve (early infection) or a ring corneal infiltrate	Culture (on special media)	For *Acanthamoeba*: first-line treatment is with topical chlorhexidine and polyhexamethylene biguanide; systemic voriconazole and miltefosine have been added for cases refractory to topical therapy [9].

Table 3. Continued

Syndromes	Pathogens	Exam Features	Diagnostic Tests	Treatment
Herpes zoster ophthalmicus	VZV	Vesicles on eyelids, conjunctivitis, iritis, keratitis; slit lamp exam shows epithelial pseudo-dendrites or stromal infiltrates	Skin lesions can be sampled for molecular diagnostics or culture; the diagnosis is often made clinically	Same as for herpes zoster: in most patients, oral antiviral agents (acyclovir 800 mg, 5 times daily, famciclovir 500 mg tid, or valacyclovir 1000 mg tid) × 7 d. For immunocompromised patients or for disseminated zoster, IV acyclovir 10 mg/kg q8 h, then after improvement, valacyclovir 1000 mg po tid, total duration usually 7–14 d. For retinal involvement, see "acute retinal necrosis."
HSV keratitis	HSV	On slit lamp exam, dendritic corneal epithelial infiltrate on fluorescein staining, or stromal infiltrate	Corneal scraping under slit lamp (by ophthalmologist) of epithelial lesions can be sampled for molecular diagnostics or culture, but the diagnosis is often made clinically	HSV epithelial keratitis: topical or oral antivirals; HSV stromal keratitis: topical corticosteroids plus oral antiviral agents. Oral antiviral agents include acyclovir 400–800 mg 5 times daily × 7–10 d), famciclovir (500 mg bid × 7–10 d), or valacyclovir 1000–2000 mg PO tid 7–10 d. Topical agents include trifluridine 1% q1–2 h × 14 d, ganciclovir 0.15% 5 times daily until epithelial healing, then tid × 1 wk. Chronic acyclovir (400 mg twice daily), famciclovir (250 mg twice daily), or valacyclovir (500 mg once daily) reduces the recurrent rates of HSV keratitis [10–12].

This table is not meant to be comprehensive, and treatment should be individualized to the patient.

Abbreviations: bid, twice daily; HSV, herpes simplex virus; IM, intramuscular; IV, intravenous; PCR, polymerase chain reaction; PO, per oral (by mouth); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; tid, 3 times daily; VZV, varicella zoster virus.

The treatment of exogenous endophthalmitis includes intravitreal injections of antibiotics (Table 4). Vitrectomy is performed as an initial procedure in severe cases or in cases that are refractory to intravitreal injections. Adjunctive systemic antibiotics are typically not given in exogenous endophthalmitis except in fungal endophthalmitis, where an oral azole (eg, fluconazole or voriconazole) is often added.

Endogenous endophthalmitis accounts for less than 15% of all endophthalmitis cases, but an ID specialist is likely to help manage these infections. Patients may or may not have systemic symptoms at the time of presentation; in some cases, endophthalmitis results from transient bacteremia or fungemia. Importantly, fevers may be absent. Common sources of endogenous bacterial endophthalmitis include endocarditis, urinary tract infections, liver abscesses, and gastrointestinal procedures. The most common pathogens are *Staphylococcus aureus*, streptococci, *Escherichia coli*, and hypermucoviscous *Klebsiella pneumoniae*. This last organism is associated with a syndrome of liver abscess, initially described in southeast Asia over 35 years ago but more recently reported in locations worldwide [25].

The most important initial treatment of endogenous endophthalmitis to attempt to preserve vision is the intravitreal injection of antimicrobials; vitrectomy is added for severe cases. Systemic antibiotics are always given to treat the associated systemic infection, which determines the duration of systemic antibiotics (eg, 6 weeks for endocarditis). The choice of systemic antibiotics should reflect the goal of optimizing intraocular drug levels while also providing optimal treatment for the systemic infection. Intravenous (IV) vancomycin, ceftriaxone, ceftazidime, and carbapenems are among the IV antibiotics likely to achieve good intraocular (aqueous, vitreous) levels. Oral antibiotics that are likely to achieve good levels in the eye include fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX), and linezolid, but data are limited for most antibiotics in human eyes [26]. The visual outcomes from endogenous bacterial endophthalmitis are poor due to the virulence of the usual pathogens of the bacteremia; vitrectomy may improve the visual prognosis [27].

Compared with bacteremia, candidemia poses a much higher risk for ocular seeding, associated with chorioretinitis in 9.2% and progression to endophthalmitis in 1.6% of cases in a large prospective trial [28]. Common risk factors for endogenous fungal endophthalmitis in hospitalized patients are the same as for fungemia (eg, central venous catheters, severe immunocompromise). In outpatients, IDU and current or recent central venous catheters are major risk factors. *Candida* spp. are the most common pathogens. Molds such as *Aspergillus* and *Fusarium* are occasional pathogens. The Infectious Diseases Society of America (IDSA) advises at least 4 to 6 weeks of systemic antifungal therapy with voriconazole or fluconazole (for azole-resistant isolates, liposomal amphotericin

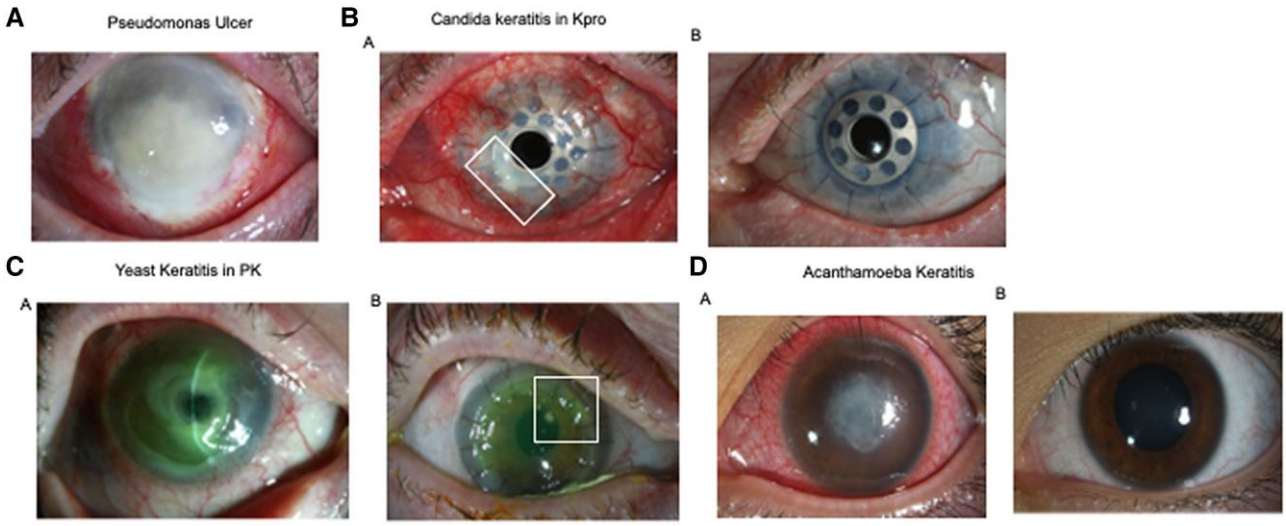


Figure 3. Microbial keratitis. *A, Pseudomonas* ulcer. A 92-year-old patient presented with 1 month of eye pain and redness. Corneal cultures grew abundant pan-sensitive *Pseudomonas aeruginosa*. Note the conjunctival injection (redness), soupy and suppurative appearance of the cornea, and loss/thinning of peripheral corneal tissue. *B, Candida* keratitis in Kpro. A 74-year-old patient with a history of ocular trauma, now with a keratoprosthesis (Kpro; artificial cornea) in his only eye, developed foreign body sensation and conjunctival injection. Exam revealed a white corneal infiltrate from 6 to 9 o'clock underneath the Kpro front plate, with associated thinning ("A", white box). Corneal culture confirmed *Candida albicans*. The fungal infiltrate persisted despite topical amphotericin and oral fluconazole, and the Kpro was replaced ("B", 4 months post-operatively). *C,* Yeast keratitis in penetrating keratoplasty (PK). An 80-year-old woman was referred with infectious keratitis (*Klebsiella oxytoca* by report). She developed significant corneal thinning ("A") and a tectonic penetrating keratoplasty (corneal transplant) was performed. She subsequently developed multifocal white corneal opacities in the keratoplasty ("B", white box) that were cultured and grew *Candida parapsilosis*. *D, Acanthamoeba* keratitis. A 12-year-old contact lens-wearer developed *Acanthamoeba* keratitis ("A"). Topical polyhexamethylene biguanide and chlorhexidine were initiated every 2 hours with gradual taper over the course of 3 months, with resolution of infection and resultant corneal stromal scarring ("B").

with or without flucytosine) for patients with ocular candidiasis, with the addition of intravitreal injections of amphotericin or voriconazole and consideration of vitrectomy for macula-threatening chorioretinitis or endophthalmitis [24]. Echinocandins likely achieve good levels in the highly vascular choroid. However, unlike fluconazole and voriconazole, echinocandins do not achieve good concentrations in the aqueous and vitreous [29]. A switch from an echinocandin to fluconazole (for susceptible *Candida* species) or voriconazole is recommended for ocular candidiasis (chorioretinitis or endophthalmitis). In endogenous *Candida* endophthalmitis, the visual outcomes are often good if the diagnosis is made early.

Since chorioretinitis typically is asymptomatic unless there is macular involvement, the vast majority of candidemic patients (>80%) lack ocular symptoms at the time they are diagnosed with ocular candidiasis by a screening exam [30]. Because ocular disease influences the choice of antifungal drug, duration of systemic antifungal treatment, and need for ophthalmologic follow-up exams, even for chorioretinitis alone, IDSA guidelines recommend eye examinations in all patients with candidemia. The American Academy of Ophthalmology is in concordance that eye examinations should be performed if there are ocular signs or symptoms but does not recommend eye examinations in asymptomatic patients with candidemia [31]. The impact of this recommendation on rates and outcomes of ocular candidiasis is an important area for investigation.

Endophthalmitis Associated With Injection Drug Use

Injection drug use has been an increasing cause of morbidity and mortality over the last several decades, due to risks from overdose and serious injection-related infections [32], including endogenous endophthalmitis. Most IDU-associated endophthalmitis cases are due to fungal infections, primarily *Candida* spp., and more rarely *Aspergillus* spp. [33–35]. However, bacterial etiologies make up a substantial minority of cases [36, 37]. In a series from a tertiary care referral center in Boston between 2006 and 2014, IDU-associated endophthalmitis represented 9% of all patients with endophthalmitis and 44% of patients with endogenous endophthalmitis. Of these infections, 59% were fungal, 16% bacterial, and the rest were either culture negative or refused culture [36].

In addition to intravitreal antimicrobials and procedural management, systemic antimicrobials must be chosen carefully to maximize intraocular penetration and manage drug interactions. Patients taking methadone and azoles concurrently require close QTc monitoring; azoles may increase methadone serum levels, requiring possible dose titration [38–40]. Management of IDU-associated endophthalmitis would likely benefit from a multidisciplinary team approach including Ophthalmology, ID, and Addiction Medicine [32, 41, 42].

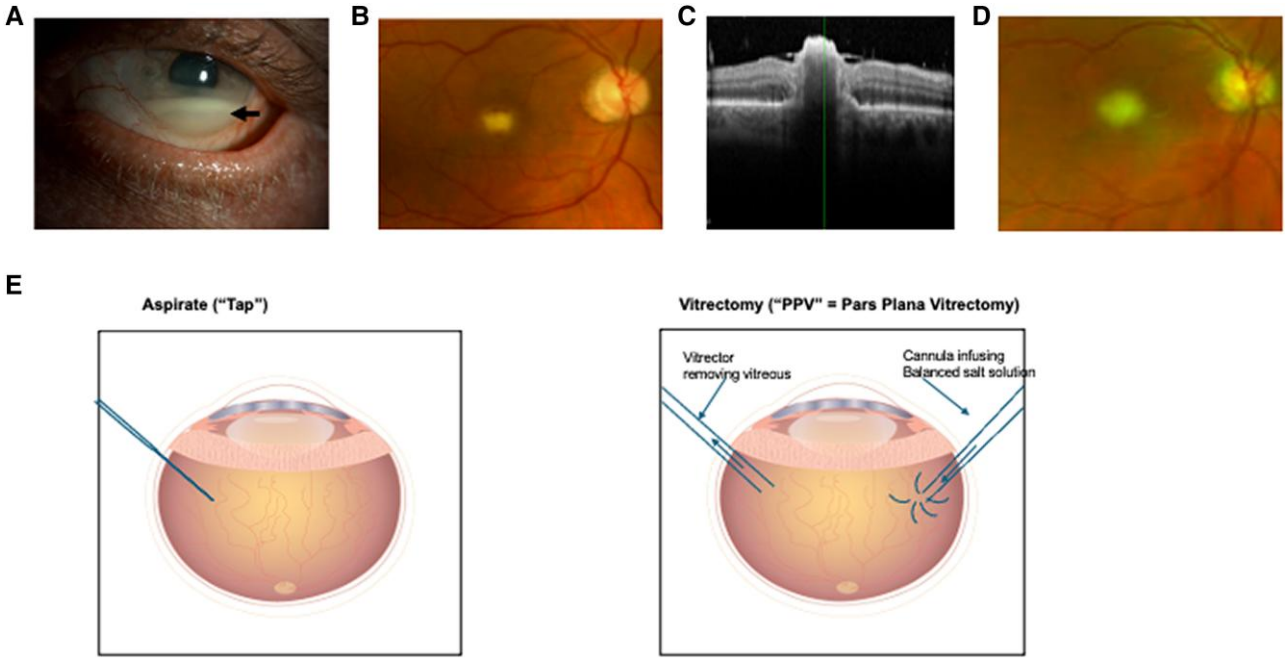


Figure 4. Endophthalmitis. *A*, Fungal endophthalmitis. Penlight exam shows a hypopyon (arrow), a collection of pus in the anterior chamber, in a patient who initially had a corneal ulceration that subsequently progressed. A culture sample from the aqueous humor grew *Candida albicans*. *B*, Occult endogenous *Candida* chorioretinitis following lithotripsy. The photo shows a white, elevated, and fluffy chorioretinal lesion; urine culture grew *C albicans* [20] (https//:creativecommons.org/licenses/by/4.0; no changes were made). *C*, Optical coherence tomography (OCT) imaging of refractory *Candida* chorioretinitis in the patient from panel *B*, progressing to endogenous endophthalmitis, with an elevated, hyperreflective foveal lesion at the vitreoretinal interface [20] (https//:creativecommons.org/licenses/by/4.0; no changes were made). *D*, Color fundus photography 2 weeks after panel *C*, displaying significant vitritis that obscures retinal detail [20] (https//:creativecommons.org/licenses/by/4.0; no changes were made). The patient subsequently underwent vitrectomy due to persistent vitritis despite intravitreal and systemic antifungal therapy. *E*, Ocular samples for diagnostic testing can be obtained by a "tap and inject," in which a vitreous sample is collected in a procedure room and antimicrobials are then injected into the vitreous, or a vitrectomy, which is a surgical procedure performed under regional block anesthesia (antibiotics are injected into the vitreous at the end of the case). Vitrectomy has the benefit of both allowing debridement of infected vitreous and providing a larger sample for diagnostic studies, which can include organism stains, cultures, and molecular testing. The risks of vitrectomy include intraocular hemorrhage, infection, retinal damage or detachment, and cataract development/progression. The risks of hemorrhage, infection, or retinal detachment are very low. Importantly, endophthalmitis is often a clinical diagnosis as both types of samples have imperfect sensitivity.

UVEITIS/RETINITIS

Herpesviral Anterior and Posterior Uveitis

Vignette

A 54-year-old man without a significant prior medical history presents with 5 days of mild eye pain and progressively blurry vision and floaters OS. Flashlight examination is normal, but visual acuity OS is 20/200. Dilated funduscopic examination reveals retinal necrosis and vasculitis with associated vitritis (Figure 5). He is diagnosed with acute retinal necrosis (ARN). A vitreous aspirate is sent for polymerase chain reaction (PCR) testing for HSV and VZV. He receives an intravitreal injection of foscarnet and starts high-dose oral valacyclovir with close outpatient follow-up. Two days later, the retinitis has progressed, and he is admitted for IV acyclovir. The vitreous PCR testing shows VZV.

Herpes simplex virus is the most common infectious cause of anterior uveitis (inflammation of the ciliary body and iris, typically also involving the aqueous humor), but approximately 90% of anterior uveitis cases have a noninfectious etiology. Anterior uveitis is less likely to cause permanent vision loss than posterior uveitis (inflammation of the choroid, often involving the retina and vitreous) or panuveitis (inflammation involving anterior and posterior segments of the eye).

Acute retinal necrosis and progressive outer retinal necrosis (PORN) are types of posterior uveitis usually caused by VZV or HSV. These very rare infections are ophthalmologic emergencies as they can rapidly cause irreversible vision loss via a vasoocclusive angiitis of retinal and choroidal vessels, preferentially affecting the peripheral retina in ARN and the posterior pole faster in PORN. Acute retinal necrosis may also present as a panuveitis. Symptoms of both ARN and PORN include rapid onset of decline in or dimming of vision, sometimes with eye redness, photophobia, floaters, and pain [43].

Typically caused by HSV or VZV, ARN may be unilateral or bilateral. Most patients have no active extraocular herpesvirus infection and no obvious immune deficiency. Distinct from the syndrome of cytomegalovirus (CMV) retinitis, ARN can be caused by CMV in hosts with either local (eg, ocular

Table 4. Clinical Syndromes, Causative Pathogens, and Treatment Strategies for Infections Causing Uveitis and/or Vitritis (Medication Doses Assume Normal Renal Function)

Syndromes	Pathogens	Exam Features	Diagnostic Tests	Treatment
CMV retinitis	CMV	Hemorrhages, retinal infiltrate, and may include perivascular exudates and a granular appearance to the retinitis. There is typically minimal vitritis	Serum/ocular fluid PCR, serologies	2–3 wk induction with ganciclovir 5 mg/kg IV q12 h or oral valganciclovir 900 mg PO q12 h; followed by suppressive valganciclovir 900 mg PO daily thereafter, prolonged: eg, 3–6 m. Intravitreal foscarnet. ID input may be helpful for systemic disease workup and treatment.
Acute retinal necrosis (ARN)	VZV, HSV (very rarely CMV, in immunocompromised hosts)	ARN: confluent areas of necrotizing retinitis, most often in the periphery initially	Clinical appearance, PCR of aqueous or vitreous	Acyclovir 10–15 mg IV q8 h induction, then valacyclovir 1–2 g PO tid, usually given for at least 6 wk. In many patients with early ARN, high-dose oral valacyclovir (eg, 2 g q8 h) may be given as initial treatment. Intravitreal foscarnet is usually given along with valacyclovir or IV acyclovir. Lifelong suppression with acyclovir 400 mg bid is sometimes then given (particularly for immunosuppressed patients). Systemic corticosteroids may be used as adjunctive therapy, typically added (when needed) only after an initial few days of antiviral therapy. Intravitreal foscarnet (see above; injections may be repeated). Intravenous foscarnet may be considered in refractory cases [22].
Progressive outer retinal necrosis (PORN)	VZV (mostly), HSV	Similar to ARN, early involvement of the macula		PORN management is on a case-by-case basis, including intravitreal and IV antivirals and efforts to improve immune function. ID input may be helpful.
Toxoplasmosis	*Toxoplasma gondii*	New, creamy-white active lesion typically adjacent to an old scar; view is often hazy due to vitritis	Clinical exam, serologies, ocular samples for PCR	First-line treatments are as follows: 1. Pyrimethamine (100 mg PO on day 1 then 25–50 mg PO once daily) plus sulfadiazine (1 g PO every 6 h) with folinic acid, 10–20 mg PO once daily, to prevent bone marrow suppression, or 2. Trimethoprim-sulfamethoxazole 160 mg trimethoprim–800 mg sulfamethoxazole. 5-10 mg/kg/d (trimethoprim component) in divided doses Adjunctive/alternative therapies in patients with sulfa allergy or refractory disease: 1. Intravitreal clindamycin (1 mg/0.1 mL), plus intravitreal dexamethasone; injections may be repeated. 2. Oral azithromycin, 250–500 mg daily (uncertain efficacy, very small studies, see text). 3. Oral atovaquone, 750 mg PO 4× daily [23] (uncertain efficacy, very small studies, see text). –Oral prednisone (eg, 0.5–1 mg/kg once daily initially, tapered with clinical response) is often added to any regimen to treat the intraocular inflammation.

Table 4. Continued

Syndromes	Pathogens	Exam Features	Diagnostic Tests	Treatment
Ocular syphilis	*Treponema pallidum pallidum*	All parts of the eye can be affected but uveitis is most common	Treponemal and nontreponemal serologies, though nontreponemal testing may be negative in ocular syphilis	–Aqueous crystalline penicillin G, 18–24 million units per day, administered as 3–4 million units IV every 4 h or continuous infusion for 10–14 d or –Procaine penicillin G, 2.4 million units IM once daily plus probenecid 500 mg orally 4 times/d, both for 10–14 d. –After definitive therapy (above), benzathine penicillin, 2.4 million units IM once per week for 1–3 wk, can be given to treat any residual treponemes from latent syphilis. [5]
Exogenous endophthalmitis (most commonly, postsurgical or posttraumatic)	Staphylococci, streptococci, *Bacillus cereus*, fungi	Endophthalmitis, usually with hypopyon in bacterial cases	Clinical exam/history, ocular cultures	Intravitreal antibiotic injections (empirically vancomycin/ceftazidime for bacterial cases; amphotericin or voriconazole for suspected fungal infection). Systemic agents are often included in fungal cases. Intracameral injections (into the anterior chamber) are added in some cases (eg, from extension of keratomycosis).
Endogenous endophthalmitis	*Staphylococcus aureus*, streptococci, *Escherichia coli*, and hypermucoviscous *Klebsiella pneumoniae* are the most common bacterial etiologies; *Candida* species are the most common fungal etiologies with IDU, indwelling IV lines, and other risks for bloodstream infection associated with risk for endogenous endophthalmitis	Endophthalmitis, usually with hypopyon	Clinical exam/history, ocular cultures, though diagnosis may be made by blood culture or culture of another site of systemic infection, such as urinary tract, sputum, or liver abscess	Intravitreal antibiotic injections (empirically vancomycin/ceftazidime for bacterial cases; amphotericin or voriconazole for suspected fungal infection). Systemic antimicrobials are included to treat the associated systemic infection, which determines the duration of systemic antibiotics (eg, 6 wk for endocarditis).
Ocular candidiasis	*Candida* spp.	Chorioretinitis, vitritis, endophthalmitis with balls of inflammation	Clinical exam/history, confirmation may be possible by stain/culture/PCR testing of ocular samples	Chorioretinitis may be treated with systemic antifungal medications alone but requires close follow-up as some cases progress to endophthalmitis despite treatment. Endogenous *Candida* endophthalmitis (ie, with vitritis) requires both intravitreal antifungal injections plus systemic therapy, the latter given for at least 4–6 wk with final endpoint determined based on clinical response, may also need vitrectomy: –Azole-susceptible strains: fluconazole 800 mg (12 mg/kg), then 400–800 mg (6–12 mg/kg) daily or voriconazole, loading dose 400 mg (6 mg/kg) intravenous twice daily for 2 doses, then 300 mg (4 mg/kg) IV or oral twice daily. Monitoring of serum drug levels may help ensure appropriate dosing. –Azole-resistant strains: liposomal AmB, 3–5 mg/kg intravenous daily, with or without oral flucytosine, 25 mg/kg 4 times daily. [24]

This table is not meant to be comprehensive, and treatment should be individualized to the patient.

Abbreviations: bid, twice daily; CMV, cytomegalovirus; HSV, herpes simplex virus; ID, infectious disease; IDU, injection drug use; IV, intravenous; PCR, polymerase chain reaction; PO, per oral (by mouth); tid, 3 times daily; VZV, varicella zoster virus.

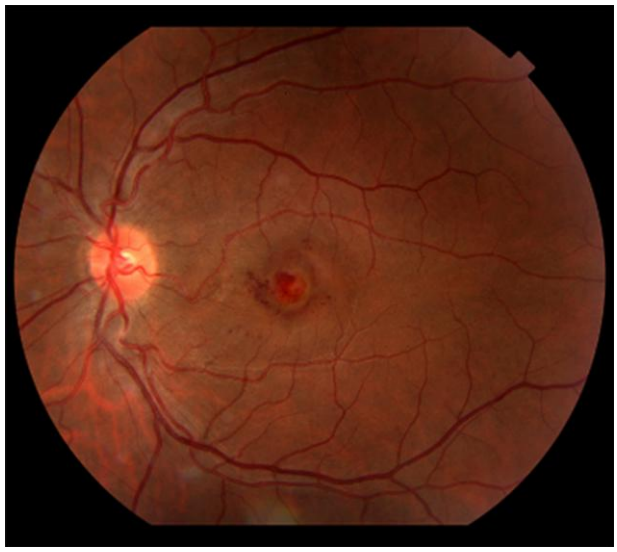


Figure 5. Acute retinal necrosis. Fundus photograph of the left eye demonstrating acute necrotizing retinitis (white areas of retina following the inferior arcade) with macular involvement demonstrated by hemorrhage and retinal edema.

corticosteroid injections) or systemic immune compromise. A role for Epstein-Barr virus (EBV) in ARN is uncertain as 20% of normal cadaveric eyes have EBV DNA in the vitreous [44].

Typically caused by VZV, PORN is a more severe syndrome most commonly affecting profoundly immunocompromised hosts, particularly patients with AIDS. Progressive outer retinal necrosis affects the peripheral retina, but the macula is involved early [45, 46].

The diagnosis of ARN or PORN is typically clinical, via a dilated funduscopic examination showing necrotizing retinitis and retinal arteritis (Table 4). Acute retinal necrosis may be associated with significant vitritis, while PORN tends to have minimal associated inflammation in the aqueous or vitreous. Polymerase chain reaction testing of aqueous or vitreous can confirm the diagnosis and has high sensitivity for identifying the viral etiology [43], but treatment is a medical emergency and should not await results. In cases caused by HSV or VZV, testing for viremia is usually negative and not routinely recommended. Serum CMV viral load should be measured if there is concern for CMV infection in immunocompromised hosts, but extraocular infection may not accompany ocular infection. Evaluation for immune deficiency, including human immunodeficiency virus (HIV) testing, should be performed for patients with ARN and PORN.

The treatment of ARN includes IV acyclovir or high-dose oral valacyclovir, plus usually intravitreal foscarnet. Intravenous acyclovir and oral valacyclovir may be similarly effective for ARN, although there have been no prospective trials for this rare disease [47]. Intravenous acyclovir is favored in cases of severe ocular disease, immune deficiency, suboptimal response to valacyclovir, high body mass index, or difficulty with monitoring in the outpatient setting. Intravitreal foscarnet provides immediate therapeutic levels in the eye and often is administered at the time of initial presentation. Intravitreal foscarnet injections may be repeated every 48–72 hours until there is stabilization of the exam [48, 49]. Most patients with ARN are immunocompetent, but in immunocompromised patients, tapering immunosuppressive medications (if possible) may be helpful. If there is concern for CMV, oral valganciclovir or IV ganciclovir should be used. The goal of treatment is to rapidly halt the progression of retinitis. If there is progression of retinitis despite first-line antiviral medications, then a switch to IV foscarnet should be considered. This approach has saved the vision of several patients [22].

Topical prednisolone can be started immediately with antivirals. Oral corticosteroids are sometimes given, beginning at least 24 to 48 hours after starting antivirals, to control the intraocular inflammation, but data are lacking regarding benefit [43]. Serial photography is often used to track progress.

Often, patients with ARN transition to oral antivirals once the exam has stabilized on IV therapy. Valacyclovir is used for HSV or VZV, typically for at least 6 weeks, but the duration is determined by the patient's clinical response. Valganciclovir is used for CMV. Cytomegalovirus ARN is typically treated for at least 3–6 months. Patients with vision-threatening HSV or VZV are often maintained on long-term antivirals. Patients with ARN from CMV may require long-term antiviral therapy, depending on their immune function.

Visual outcomes from ARN are poor. In 1 study, 48% of patients had visual acuity of 20/200 or worse at 6 months [50]. The most common cause of vision loss is retinal detachment, occurring in 30% to 73% of patients. Other causes include chronic vitritis, epiretinal membrane, macular ischemia, macular edema, and optic neuropathy [51].

Progressive outer retinal necrosis is treated with IV acyclovir or foscarnet, plus intravitreal foscarnet injections. A switch from IV acyclovir to IV foscarnet may be considered in rapidly worsening cases, as for ARN [22]. Patients with PORN are severely immunosuppressed, so the role of corticosteroids is uncertain. Progressive outer retinal necrosis is very rare and has a very poor prognosis; treatment should be on a case-by-case basis.

Toxoplasma gondii Uveitis

Vignette

A 26-year-old man presents with blurry vision OD for the last several days. He had a similar but less severe episode 3 years ago that self-resolved. He is otherwise well and has no past medical history. He emigrated to the United States from Brazil 5 years ago. His eye exam reveals a creamy-white lesion adjacent to a scar; the view is hazy due to vitritis. He is diagnosed with ocular toxoplasmosis and treated with TMP-SMX.

Toxoplasmosis is caused by the intracellular protozoan parasite *Toxoplasma gondii*. Cats are the definitive host. In serologic studies, 25%–30% of the world's population is infected, but this rate is higher in some countries than in others (eg, 11% in the United States but up to 80% in Brazil) [23, 52, 53]. Most commonly, humans acquire infection by ingesting oocysts in the environment or in contaminated food or water, eating raw or undercooked meat that contains latent tissue cysts, or in utero, usually during an acute maternal infection. Following the initial infection, which is often asymptomatic, *T gondii* establishes a chronic latent infection in various tissues.

Ocular disease is often the only manifestation of toxoplasmosis in the immunocompetent host. Toxoplasmosis is the most common cause of posterior uveitis in most series worldwide [7]. The initial episode may be asymptomatic but leaves a hyperpigmented chorioretinal scar. As in the case vignette, recurrent episodes of ocular toxoplasmosis occur in over 50% of patients [23] and manifest as a new, creamy-white active lesion typically adjacent to the old scar. The active lesion may be asymptomatic if it is in the periphery of the retina (ie, outside the macula) and does not involve the optic nerve or cause marked vitreous inflammation (Figure 6). However, vitreous inflammation is common, so the view to the fundus is often hazy. The patient typically reports decreased vision, which may be permanent if the episode affects the macula. Although the active lesion spontaneously heals and forms a scar, treatment (Table 4) is usually associated with a decrease in lesion size [23]. The most common treatment is pyrimethamine plus sulfadiazine, or TMP-SMX, with or without an intravitreal injection of clindamycin. Leucovorin (folinic acid) is given with pyrimethamine to prevent bone marrow suppression. Corticosteroids are often added to antimicrobials to treat the intraocular inflammation. There are several alternative treatments for sulfa-allergic patients or perhaps for treatment-refractory disease, but there is less experience with these treatments, and few studies compare efficacy with standard therapy. The most promising alternative therapy is the repeated intravitreal injection of clindamycin plus dexamethasone, based on the results of 2 randomized prospective trials each involving approximately 65 patients [54, 55]. Studies involving other agents, such as oral azithromycin or oral atovaquone, have been very small (most, <20 patients) [56, 57].

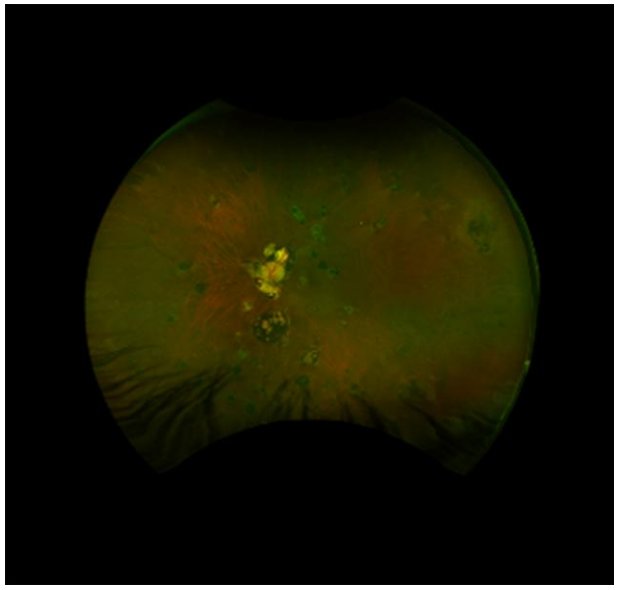


Figure 6. *Toxoplasma gondii* uveitis. Fundus photograph with multifocal chorioretinal scars in a patient with ocular toxoplasmosis. As the fovea had no direct involvement, the vision in this eye remained 20/20.

Randomized prospective trials from Brazil demonstrate the efficacy of TMP-SMX prophylaxis in preventing recurrent ocular toxoplasmosis following an acute flare. In the most recent study, following treatment with TMP-SMX for an acute flare of ocular toxoplasmosis, 141 patients were randomized to either receive placebo or to continue TMP-SMX every other day for over 300 days. After 6 years of follow-up, 28% of the placebo group had had a recurrence versus 1.4% of the antibiotic prophylaxis group [58].

Syphilitic Uveitis

Vignette

A 35-year-old man with a history of sexually transmitted infections presents with 4 days of ocular injection and blurry vision in both eyes (oculus uterque, OU) without other symptoms. Eye examination shows panuveitis OD > OS. Laboratory testing returns with rapid plasma reagin (RPR) 1:256 and positive fluorescent treponemal antibody absorption (FTA-ABS). He is admitted to begin IV penicillin for ocular syphilis and improves.

With resurging incidence in the United States and around the world [59], syphilis is playing an increasing role in eye infections, although it accounts for a small minority of all cases of uveitis. There were more than 200 000 cases of syphilis in the United States in 2022, which is nearly double that of 2018 [60]. A small proportion (1.7%–2.5%) of patients with syphilis report ocular or neurologic symptoms [61], but involvement of the eye can result in debilitating sequelae if not diagnosed and managed properly. Syphilis can involve any part of the eye. It most commonly manifests as posterior uveitis, panuveitis, and anterior uveitis (Figure 7). Patients' most common presenting complaint is diminished visual acuity in 1 or both eyes. Ocular syphilis occurs most commonly in secondary syphilis (~3–6 months following infection) and may be accompanied by additional symptoms and findings, such as rash and lymphadenopathy. However, many patients with ocular syphilis, including those with late-stage syphilis, have no concurrent symptoms. The diagnosis of ocular syphilis relies on compatible ophthalmologic exam findings and a positive serum

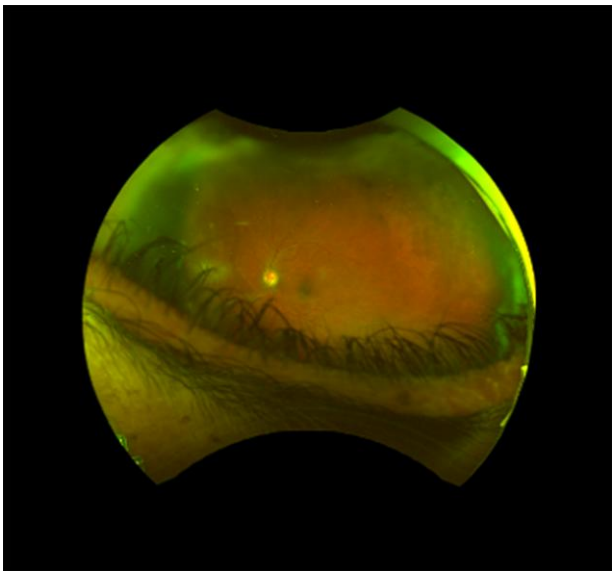


Figure 7. Ocular syphilis. Fundus photograph of a patient who presented complaining about blurry vision OS. On exam, the view is somewhat hazy due to vitritis but demonstrates retinal vascular sheathing. Her nontreponemal test (RPR) and treponemal test (FTA-ABS) were positive. Abbreviations: FTA-ABS, fluorescent treponemal antibody absorption; OS, oculus sinister (left eye); RPR, rapid plasma reagin.

treponemal test. Importantly, ocular syphilis may occur in people with negative or low-titer non-treponemal tests (eg, RPR) [62, 63], so treponemal testing is an important part of the diagnostic strategy for ocular syphilis. Patients with a negative RPR, positive treponemal test, and no prior syphilis infection history should have confirmation with a second positive treponemal test (ideally the *Treponema pallidum* particle agglutination assay [TPPA], which is the most accurate). False-negative RPR testing can occur in the setting of very high antibody levels that interfere with the formation of the antibody–antigen lattice that leads to the precipitation that defines a positive test. In cases of strong clinical suspicion for syphilis with negative RPR testing, the test should be repeated with further dilutions of the sample [64].

Cerebrospinal fluid (CSF) examination is not necessary to make the diagnosis of ocular syphilis, but up to 60% of people with ocular syphilis have abnormal CSF testing, and this is likely more common in people with HIV [65]. Updated recommendations from the US Centers for Disease Control and Prevention state that a lumbar puncture is unnecessary before treatment "among persons with isolated ocular symptoms (ie, no cranial nerve dysfunction or other neurologic abnormalities), confirmed ocular abnormalities on examination, and reactive syphilis serology" [5]. All patients with ocular syphilis should undergo HIV testing and screening for other sexually transmitted infections. Treatment for ocular syphilis is the same as for neurosyphilis (Table 4). A recent multicenter retrospective study of patients with ocular and neurosyphilis suggested that ceftriaxone could be a reasonable alternative to IV penicillin, although study design limitations and the nonrandomized nature of treatment allocation may limit these findings' applicability to general practice [66]. Many patients with uveitis due to ocular syphilis gain some early benefit from topical corticosteroids. Oral corticosteroids are often given in cases with significant intraocular inflammation but have not been evaluated in randomized controlled trials. Symptoms of ocular syphilis typically improve quickly, but monitoring of serologies following treatment is important to ensure an adequate response to treatment, including response of any concomitant neurosyphilis.

Tuberculous Uveitis

Vignette

A 67-year-old woman is referred to an ID clinic after positive interferon-gamma release assay (IGRA) testing. She has uveitis that has been incompletely responsive to variable doses of topical steroids over 6 months. Systemic immune suppression is being considered. She received bacille Calmette-Guerin (BCG) vaccine as a child in a high-tuberculosis (-TB)–burden country but is not aware of any TB exposures. She emigrated to the United States 12 years prior to presentation. She has no symptoms other than blurry vision. Her chest radiograph is normal.

Uveitis occurs in approximately 1.5% of patients with systemic TB [67] and is diagnostically challenging. Sampling for microbiological confirmation has low yield. Most cases are diagnosed and treated presumptively [68]. In the absence of high-quality evidence, current diagnostic and management approaches are based on expert opinion [69–71].

Presumptive diagnoses consider exam features, history, IGRA or tuberculin skin testing (TST), evidence of systemic disease, and lack of an alternative etiology for ocular disease. Ocular exam features may be suggestive but are not specific. Tuberculosis can infect any ocular tissue but particularly affects the choroid. Serpiginous-like choroiditis, choroid tuberculoma/tubercles (Figure 8), or multifocal choroiditis are all suggestive of TB [73]. In serpiginous-like choroiditis, lesions are very rarely (<15% of cases) contiguous with the optic disc [7], while in serpiginous choroiditis, an idiopathic inflammatory process, lesions extend from around the optic nerve into the macula [74, 75]. Choroid tubercles are a helpful exam finding, but sarcoidosis, syphilis, metastatic cancer, and other entities can appear similar to TB tubercules. Usually there are fewer than 5 choroid tubercles [76]. Other findings in ocular TB include retinal vasculitis (Eales disease) and granulomatous anterior uveitis.

By history, recurrent episodes of uveitis may be suggestive of TB in the appropriate host [70]. Importantly, a uveitis response to topical or systemic steroids does not rule out TB, as TB will initially respond to the immunomodulating effects of steroids [77]. A TB exposure history, with or without positive IGRA or TST testing, can support the diagnosis but is very

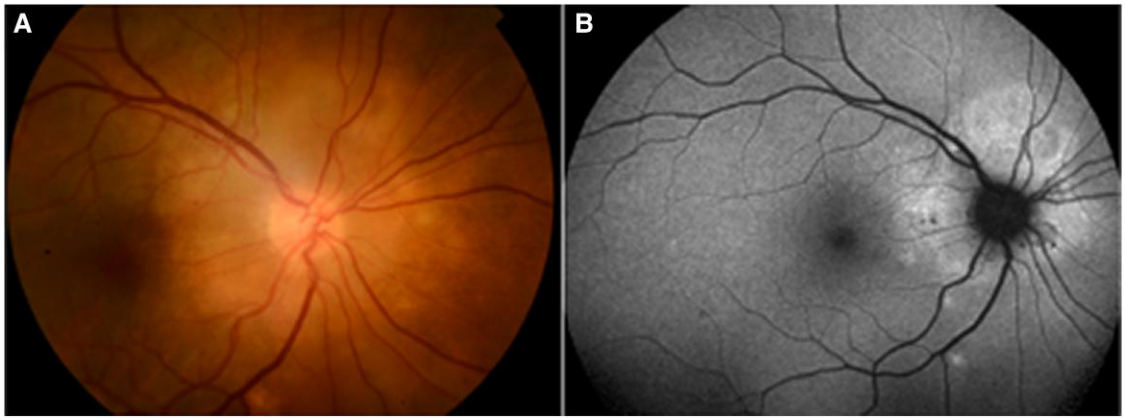


Figure 8. Ocular tuberculosis. Tubercles. Fundus photo (*A*) shows the presence of multiple, yellowish lesions with indistinct borders. Edema around the optic disc (*A*) is better evidenced with (*B*) hyperfluorescent on fundus autofluorescence imaging [72] (https://creativecommons.org/licenses/by/4.0/; no changes were made).

nonspecific, especially for patients who have lived in TB-endemic regions [78–81]. Chest computed tomography (CT) should be performed if an initial chest X-ray is normal. Although many series report that most patients with presumed TB uveitis do not have concurrent pulmonary TB, these patients did not undergo chest CT [70, 78, 82]. In addition, the diagnosis of presumed TB uveitis in these studies is uncertain, as nearly all patients were treated with both corticosteroids and anti-TB medications at the time of diagnosis. Therefore, an apparent response to "anti-TB therapy" may instead reflect a response of a noninfectious uveitis to corticosteroids given concurrently. When the patient is otherwise asymptomatic and has a normal chest CT, the decision to treat must be considered on a case-by-case basis. Some ID specialists also check first-morning urine samples or abdominal CT imaging to exclude concurrent renal TB, although renal TB is very rare. When there is no evidence of extraocular TB, the diagnosis of ocular TB can only be presumptive. Except in miliary TB, ocular cultures for TB are typically negative. The organisms are most likely in the choroid, which cannot be safely biopsied. In addition, pathologic studies have shown that there may be very few organisms in the choroid [83]. The sensitivity of molecular testing of aqueous or vitreous is uncertain as false-positive and false-negative results have been described. This is an area of active investigation [84, 85].

Empiric treatment regimens are similar to those used for other forms of drug-susceptible TB. The intensive phase includes rifampin, isoniazid, pyrazinamide, and ethambutol for 2 months [86], followed by rifampin and isoniazid in the continuation phase for an additional 4 months. Some providers choose to replace ethambutol with moxifloxacin to avoid risks of ocular toxicity from ethambutol [87]. In patients with a positive culture for TB from an extraocular site, antibiotics are tailored to the susceptibilities of that isolate. While the clinical response to TB treatment is sometimes used as a diagnostic strategy, patients can have paradoxical worsening of inflammation after starting TB treatment [88], which can be managed with corticosteroids. Ophthalmologists may start corticosteroids at the time of TB treatment initiation to treat the inflammation from uveitis (which itself may be damaging to the retina) and to prevent paradoxical worsening, depending on the location and extent of eye findings [77, 82].

CONCLUSIONS

Ocular infections are common and range from mild to vision-threatening. They can occur independently or as a manifestation or complication of a systemic infection that can cause extraocular morbidity and even mortality. There are many challenges in diagnosing and treating ocular infections that can benefit both from collaborative care between ophthalmologists and ID specialists, as well as from efforts to collaboratively set and carry out a research agenda to improve the outcomes of these infections.

Notes

Author contributions. All authors contributed to conceiving, writing, and editing the manuscript.

Financial support. This work was supported by the National Institutes of Health (grant number K08EY031759 to T. H. D.).

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Three_Main_Layers_of_the_Eye.png (765×599). Available at: https://upload.wikimedia.org/wikipedia/commons/d/d0/Three_Main_Layers_of_the_Eye.png. Accessed 22 June 2024.
2. Jeong Y, Hong YJ, Han JH. Review of machine learning applications using retinal fundus images. Diagnostics (Basel) **2022**; 12:134.
3. Dendritic_corneal_ulcer.jpg. Available at: https://upload.wikimedia.org/wikipedia/commons/9/95/Dendritic_corneal_ulcer.jpg.
4. Azari AA, Arabi A. Conjunctivitis: a systematic review. J Ophthalmic Vis Res **2020**; 15:372–95.

5. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep **2021**; 70:1–187.
6. Parikh SR, Campbell H, Mandal S, Ramsay ME, Ladhani SN. Primary meningococcal conjunctivitis: summary of evidence for the clinical and public health management of cases and close contacts. J Infect **2019**; 79:490–4.
7. Durand ML, Barshak MB, Sobrin L. Eye infections. N Engl J Med **2023**; 389:2363–75.
8. Kiernan M. Case 14-2023: a man with redness of the right eye. N Engl J Med **2023**; 389:383–4.
9. Kaufman AR, Tu EY. Advances in the management of Acanthamoeba keratitis: a review of the literature and synthesized algorithmic approach. Ocul Surf **2022**; 25: 26–36.
10. American Academy of Ophthalmology. Herpes simplex virus keratitis: a treatment guideline—2014. Published 27 June 2014. Available at: https://www.aao.org/education/clinical-statement/herpes-simplex-virus-keratitis-treatment-guideline. Accessed 2 April 2024.
11. Wilhelmus KR, Gee L, Hauck WW, et al. Herpetic eye disease study. A controlled trial of topical corticosteroids for herpes simplex stromal keratitis. Ophthalmology **1994**; 101:1883–95; discussion 1895–96.
12. Herpetic Eye Disease Study Group. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. Available at: https://oce.ovid.com/article/00006024-199807300-00003. Accessed 18 February 2024.
13. Cope JR, Collier SA, Rao MM, et al. Contact lens wearer demographics and risk behaviors for contact lens-related eye infections—United States, 2014. MMWR Morb Mortal Wkly Rep **2015**; 64:865–70.
14. Grossman MK, Rankin DA, Maloney M, et al. Extensively drug-resistant *Pseudomonas aeruginosa* outbreak associated with artificial tears. Clin Infect Dis **2024**; 79:6–14.
15. Brown L, Leck AK, Gichangi M, Burton MJ, Denning DW. The global incidence and diagnosis of fungal keratitis. Lancet Infect Dis **2021**; 21:e49–57.
16. Dooling KL, Guo A, Patel M, et al. Recommendations of the advisory committee on immunization practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep **2018**; 67:103–8.
17. Veugen JMJ, Dunker SL, Wolffs PFG, et al. Corneal transplantation for infectious keratitis: a prospective Dutch Registry Study. Cornea **2023**; 42:1414–21.
18. Said DG, Rallis KI, Al-Aqaba MA, Ting DSJ, Dua HS. Surgical management of infectious keratitis. Ocul Surf **2023**; 28:401–12.
19. Traish AS, Chodosh J. Expanding application of the Boston type I keratoprosthesis due to advances in design and improved post-operative therapeutic strategies. Semin Ophthalmol **2010**; 25:239–43.
20. Lavine JA, Mititelu M. Multimodal imaging of refractory Candida chorioretinitis progressing to endogenous endophthalmitis. J Ophthalmic Inflamm Infect **2015**; 5:54.
21. Andreoli CM, Andreoli MT, Kloek CE, Ahuero AE, Vavvas D, Durand ML. Low rate of endophthalmitis in a large series of open globe injuries. Am J Ophthalmol **2009**; 147:601–608.e2.
22. Stryjewski TP, Scott NL, Barshak MB, et al. Treatment of refractory acute retinal necrosis with intravenous foscarnet or cidofovir. Ocul Immunol Inflamm **2018**; 26:199–203.
23. Dunay IR, Gajurel K, Dhakal R, Liesenfeld O, Montoya JG. Treatment of toxoplasmosis: historical perspective, animal models, and current clinical practice. Clin Microbiol Rev **2018**; 31:e00057-17.
24. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **2016**; 62:e1–50.
25. Martellosio JP, Gastli N, Farhat R, et al. Hypervirulent *Klebsiella Pneumoniae*, an emerging cause of endogenous endophthalmitis in a French center: a comparative cohort study. Ocul Immunol Inflammation **2023**; 31:905–13.
26. Brockhaus L, Goldblum D, Eggenschwiler L, Zimmerli S, Marzolini C. Revisiting systemic treatment of bacterial endophthalmitis: a review of intravitreal penetration of systemic antibiotics. Clin Microbiol Infect **2019**; 25:1364–9.
27. Jackson TL, Paraskevopoulos T, Georgalas I. Systematic review of 342 cases of endogenous bacterial endophthalmitis. Surv Ophthalmol **2014**; 59:627–35.
28. Phongkhun K, Pothikamjorn T, Srisurapanont K, et al. Prevalence of ocular candidiasis and *Candida* endophthalmitis in patients with candidemia: a systematic review and meta-analysis. Clin Infect Dis **2023**; 76:1738–49.
29. Ashley ESD, Lewis R, Lewis JS, Martin C, Andes D. Pharmacology of systemic antifungal agents. Clin Infect Dis. Available at: https://academic.oup.com/cid/article/43/Supplement_1/S28/318707. Accessed 10 March 2024
30. Son HJ, Kim MJ, Lee S, et al. Risk factors and outcomes of patients with ocular involvement of candidemia. PLoS One **2019**; 14:e0222356.
31. Breazzano MP, Bond JB, Bearelly S, et al. American Academy of Ophthalmology recommendations on screening for endogenous Candida endophthalmitis. Ophthalmology **2022**; 129:73–6.
32. Serota DP, Barocas JA, Springer SA. Infectious complications of addiction: a call for a new subspecialty within infectious diseases. Clin Infect Dis **2020**; 70:968–72.
33. Centers for Disease Control and Prevention (CDC). Aspergillus endophthalmitis in intravenous-drug users—Kentucky. MMWR Morb Mortal Wkly Rep **1990**; 39: 48–9.
34. Tirpack AR, Duker JS, Baumal CR. An outbreak of endogenous fungal endophthalmitis among intravenous drug abusers in New England. JAMA Ophthalmol **2017**; 135:534–40.
35. Connell PP, O'Neill EC, Amirul Islam FM, et al. Endogenous endophthalmitis associated with intravenous drug abuse: seven-year experience at a tertiary referral center. Retina **2010**; 30:1721–5.
36. Modjtahedi BS, Finn AP, Papakostas TD, Durand M, Husain D, Eliott D. Intravenous drug use-associated endophthalmitis. Ophthalmol Retina **2017**; 1: 192–9.
37. Kumar N, Garg N, Kumar N, Van Wagoner N. Bacillus cereus panophthalmitis associated with injection drug use. Int J Infect Dis **2014**; 26:165–6.
38. Cobb MN, Desai J, Brown LS, Zannikos PN, Rainey PM. The effect of fluconazole on the clinical pharmacokinetics of methadone. Clin Pharmacol Ther **1998**; 63:655–62.
39. Tarumi Y, Pereira J, Watanabe S. Methadone and fluconazole: respiratory depression by drug interaction. J Pain Symptom Manage **2002**; 23:148–53.
40. Moody DE, Liu F, Fang WB. Azole antifungal inhibition of buprenorphine, methadone and oxycodone in vitro metabolism. J Anal Toxicol **2015**; 39:374–86.
41. Paras ML, Wolfe SB, Bearnot B, et al. Multidisciplinary team approach to confront the challenge of drug use-associated infective endocarditis. J Thorac Cardiovasc Surg **2023**; 166:457–464.e1.
42. Weimer MB, Falker CG, Seval N, et al. The need for multidisciplinary hospital teams for injection drug use-related infective endocarditis. J Addict Med **2022**; 16:375–8.
43. Lains I, Eliott D. Challenges and updates on the management of acute retinal necrosis. Int Ophthalmol Clin **2022**; 62:173–96.
44. Chodosh J, Gan YJ, Sixbey JW. Detection of Epstein-Barr virus genome in ocular tissues. Ophthalmology **1996**; 103:687–90.
45. Pavesio CE, Mitchell SM, Barton K, Schwartz SD, Towler HM, Lightman S. Progressive outer retinal necrosis (PORN) in AIDS patients: a different appearance of varicella-zoster retinitis. Eye (Lond) **1995**; 9:271–6.
46. Holland GN. The progressive outer retinal necrosis syndrome. Int Ophthalmol **1994**; 18:163–5.
47. Huynh TH, Johnson MW, Comer GM, Fish DN. Vitreous penetration of orally administered valacyclovir. Am J Ophthalmol **2008**; 145:682–6.
48. Yeh S, Suhler EB, Smith JR, et al. Combination systemic and intravitreal antiviral therapy in the management of acute retinal necrosis syndrome. Ophthalmic Surg Lasers Imaging Retina **2014**; 45:399–407.
49. Schoenberger SD, Kim SJ, Thorne JE, et al. Diagnosis and treatment of acute retinal necrosis: a report by the American Academy of Ophthalmology. Ophthalmology **2017**; 124:382–92.
50. Cochrane TF, Silvestri G, McDowell C, Foot B, McAvoy CE. Acute retinal necrosis in the United Kingdom: results of a prospective surveillance study. Eye (Lond) **2012**; 26:370–8.
51. Powell B, Wang D, Llop S, Rosen RB. Management strategies of acute retinal necrosis: current perspectives. Clin Ophthalmol **2020**; 14:1931–43.
52. Pappas G, Roussos N, Falagas ME. Toxoplasmosis snapshots: global status of *Toxoplasma gondii* seroprevalence and implications for pregnancy and congenital toxoplasmosis. Int J Parasitol **2009**; 39:1385–94.
53. Robert-Gangneux F, Dardé ML. Epidemiology of and diagnostic strategies for toxoplasmosis. Clin Microbiol Rev **2012**; 25:264–96.
54. Soheilian M, Ramezani A, Azimzadeh A, et al. Randomized trial of intravitreal clindamycin and dexamethasone versus pyrimethamine, sulfadiazine, and prednisolone in treatment of ocular toxoplasmosis. Ophthalmology **2011**; 118:134–41.
55. Baharivand N, Mahdavifard A, Fouladi RF. Intravitreal clindamycin plus dexamethasone versus classic oral therapy in toxoplasmic retinochoroiditis: a prospective randomized clinical trial. Int Ophthalmol **2013**; 33:39–46.
56. Pearson PA, Piracha AR, Sen HA, Jaffe GJ. Atovaquone for the treatment of toxoplasma retinochoroiditis in immunocompetent patients. Ophthalmology **1999**; 106:148–53.
57. Lashay A, Mirshahi A, Parandin N, et al. A prospective randomized trial of azithromycin versus trimethoprim/sulfamethoxazole in treatment of toxoplasmic retinochoroiditis. J Curr Ophthalmol **2016**; 29:120–5.
58. Fernandes Felix JP, Cavalcanti Lira RP, Grupenmacher AT, et al. Long-term results of trimethoprim-sulfamethoxazole versus placebo to reduce the risk of recurrent Toxoplasma gondii retinochoroiditis. Am J Ophthalmol **2020**; 213: 195–202.
59. Oliver SE. Ocular syphilis—eight jurisdictions, United States, 2014–2015. MMWR Morb Mortal Wkly Rep **2016**; 65:1185–8.
60. Centers for Disease Control and Prevention. Sexually transmitted infections surveillance, 2022. Published 29 January 2024. Available at: https://www.cdc.gov/std/statistics/2022/default.htm. Accessed 10 March 2024.

61. Quilter LAS, de Voux A, Amiya RM, et al. Prevalence of self-reported neurologic and ocular symptoms in early syphilis cases. Clin Infect Dis **2021**; 72: 961–7.
62. Tucker JD, Li JZ, Robbins GK, et al. Ocular syphilis among HIV-infected patients: a systematic analysis of the literature. Sex Transm Infect **2011**; 87:4–8.
63. Mohareb AM, Barshak MB, Papaliodis GN, Sobrin L, Durand ML. Ocular syphilis in patients with nonreactive RPR and positive treponemal serologies: a retrospective observational cohort study. Clin Infect Dis. **2024**:ciae354. doi:10.1093/cid/ciae354.
64. Tuddenham S, Katz SS, Ghanem KG. Syphilis laboratory guidelines: performance characteristics of nontreponemal antibody tests. Clin Infect Dis **2020**; 71:S21–42.
65. Tuddenham S, Ghanem KG. Ocular syphilis: opportunities to address important unanswered questions. Sex Transm Infect **2016**; 92:563–5.
66. Bettuzzi T, Jourdes A, Robineau O, et al. Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: a retrospective multicentre study. Lancet Infect Dis **2021**; 21:1441–7.
67. Biswas J, Badrinath SS. Ocular morbidity in patients with active systemic tuberculosis. Int Ophthalmol **1995**; 19:293–8.
68. Agarwal A, Agrawal R, Gunasekaran DV, et al. The Collaborative Ocular Tuberculosis Study (COTS)-1 report 3: polymerase chain reaction in the diagnosis and management of tubercular uveitis: global trends. Ocul Immunol Inflamm **2019**; 27:465–73.
69. Agrawal R, Testi I, Mahajan S, et al. Collaborative Ocular Tuberculosis Study consensus guidelines on the management of tubercular uveitis—report 1: guidelines for initiating antitubercular therapy in tubercular choroiditis. Ophthalmology **2021**; 128:266–76.
70. Agrawal R, Testi I, Bodaghi B, et al. Collaborative Ocular Tuberculosis Study consensus guidelines on the management of tubercular uveitis—report 2: guidelines for initiating antitubercular therapy in anterior uveitis, intermediate uveitis, panuveitis, and retinal vasculitis. Ophthalmology **2021**; 128:277–87.
71. Betzler BK, Gunasekeran DV, Kempen J, et al. The historical evolution of ocular tuberculosis: past, present, and future. Ocul Immunol Inflamm **2021**; 30:593–9.
72. Pirani V, Pelliccioni P, De Turris S, et al. The eye as a window to systemic infectious diseases: old enemies, new imaging. J Clin Med **2019**; 8:1392.
73. Agrawal R, Gunasekeran DV, Agarwal A, et al. The Collaborative Ocular Tuberculosis Study (COTS)-1: a multinational description of the spectrum of choroidal involvement in 245 patients with tubercular uveitis. Ocul Immunol Inflamm **2018**; 28: 38–48.
74. Bansal R, Gupta A, Gupta V, Dogra MR, Sharma A, Bambery P. Tubercular serpiginous-like choroiditis presenting as multifocal serpiginoid choroiditis. Ophthalmology **2012**; 119:2334–42.
75. Carreño E, Portero A, Herreras JM, Calonge M, Foster CS. Distinctive clinical features of idiopathic versus infectious serpiginous choroidopathy. Ocul Immunol Inflamm **2012**; 20:448–52.
76. Helm CJ, Holland GN. Ocular tuberculosis. Surv Ophthalmol **1993**; 38:229–56.
77. Souissi S, David T, Beral L. Steroid treatment in ocular tuberculosis: a double-edged sword? J Fr Ophtalmol **2017**; 40:126–32.
78. Lee C, Agrawal R, Pavesio C. Ocular tuberculosis—a clinical conundrum. Ocul Immunol Inflamm **2016**; 24:237–42.
79. Fernández-Zamora Y, Finamor LP, Silva LMP, S Rodrigues D, Casaroli-Marano RP, Muccioli C. Role of interferon-gamma release assay for the diagnosis and clinical follow up in ocular tuberculosis. Ocul Immunol Inflamm **2023**; 31: 304–11.
80. Ahn SJ, Kim KE, Woo SJ, Park KH. The usefulness of interferon-gamma release assay for diagnosis of tuberculosis-related uveitis in Korea. Korean J Ophthalmol **2014**; 28:226–33.
81. Ang M, Nguyen HV, Kiew SY, Chen S, Chee SP, Finkelstein E. Cost-effectiveness of alternative strategies for interferon-γ release assays and tuberculin skin test in tuberculous uveitis. Br J Ophthalmol **2015**; 99:984–9.
82. Agrawal R, Gunasekeran DV, Grant R, et al. Clinical features and outcomes of patients with tubercular uveitis treated with antitubercular therapy in the Collaborative Ocular Tuberculosis Study (COTS)-1. JAMA Ophthalmol **2017**; 135:1318–27.
83. Biswas J, Madhavan HN, Gopal L, Badrinath SS. Intraocular tuberculosis. Clinicopathologic study of five cases. Retina **1995**; 15:461–8.
84. Ludi Z, Sule AA, Samy RP, et al. Diagnosis and biomarkers for ocular tuberculosis: from the present into the future. Theranostics **2023**; 13:2088–113.
85. Tsui JK, Poon SHL, Fung NSK. Ocular manifestations and diagnosis of tuberculosis involving the uvea: a case series. Trop Dis Travel Med Vaccines **2023**; 9:20.
86. Conant MM, Vrasich CR, Wongskhaluang JV, et al. Role of the infectious disease consultant in management of patients with tuberculosis-associated ocular inflammation. Open Forum Infect Dis **2016**; 3:ofv195.
87. Potter J, Agrawal R, Barraclough C, et al. Moxifloxacin: an alternative to ethambutol for the treatment of presumed ocular tuberculosis. Ocul Immunol Inflamm **2016**; 24:508–14.
88. Ganesh SK, Abraham S, Sudharshan S. Paradoxical reactions in ocular tuberculosis. J Ophthalmic Inflamm Infect **2019**; 9:19.