TABLE 113.2 Antiviral Medications Used in Herpes Simplex Keratitis

Acute Infection

Topical or systemic medication; in the immunocompromised patient, a topical agent may be combined with a systemic agent and continued longer than the indicated period

Medication, Dosage	*Frequency*
Trifluridine (Viroptic), 1% drops	9 times daily for 7 days. May decrease dose to 5 times/day after 7 days if ulcer has healed.
Acyclovir (Zovirax), 400 mg PO[a]	tid for 14–21 days
Valacyclovir (Valtrex), 1 g PO[b]	bid for 14–21 days

Prophylaxis

Against recurrent stromal keratitis, high steroid use, and graft rejection/postoperative grafts

Medication, Dosage	*Frequency*
Acyclovir (Zovirax), 400 mg PO[a,b]	bid for 12–18 mo
Valacyclovir (Valtrex), 500 mg PO[b,c]	bid for 12–18 mo

[a]Pediatric syrup, 200 mg/tsp.
[b]Not US Food and Drug Administration–approved for this specific purpose.
[c]For use in immunocompetent hosts only.
Modified from Pavan-Langston D. Ophthalmic zoster. In: Watson C, Gershon A, eds. Herpes Zoster and Post-herpetic Neuralgia. *2nd ed. Amsterdam: Elsevier Sciences BV; 2001:119–129. Reprinted with permission from Elsevier.*

TABLE 113.3 Management of Herpes Zoster Ophthalmicus (Acute)

Antivirals

Treat for 7 days, preferably starting within 72 hours of onset of rash
- Valacyclovir (Valtrex), 1 g PO tid
- Acyclovir (Zovirax), 800 mg PO 5 times/day

Immunocompromised patients: IV acyclovir for 10 days; 10 mg/kg q8h in adults and 500 mg/m^2 q8h for children younger than 12 yr

Pain Prevention and Management

Tricyclic antidepressant (e.g., nortriptyline, desipramine), 25–75 mg PO qhs or divided dose for 3 mo (or longer, prn); start at lowest dose with antivirals or as early as possible after acute disease onset, increasing over 2–3 wk prn. Caution in patients with cardiac disease.
Nonnarcotic analgesics or short-term narcotic analgesics (e.g., oxycodone, codeine)

Dermatitis Therapy

Cool to tepid wet compresses (if tolerated) to keep dermatitis clean

Ocular Anterior Segment

Exposure keratopathy: topical antibiotic ophthalmic ointment tid
Dendritiform keratopathy: therapy for 2–3 wk (variably effective)
- 3% vidarabine ointment, *or*
- 1% trifluridine 5 times/day, *or*
- Oral antivirals (see above)

Immune keratopathy, episcleritis, scleritis, or iritis:
- Topical steroids (1%–0.125% prednisolone, 0.1% dexamethasone, or 0.2%–0.5% loteprednol), q3–4h to qid prn depending on disease severity; slow taper
- Antibiotic eyedrops or gtt/ointment prophylaxis
- Oral nonsteroidal antiinflammatory agents (e.g., ibuprofen), 400 mg PO bid–tid
- Topical antivirals unnecessary
- Cycloplegia prn for iritis: scopolamine qd

Glaucoma

Topical β-blockers (e.g., timolol or carteolol) bid
Add prn latanoprost qd, brimonidine or dorzolamide bid
No miotics (e.g., pilocarpine)
Topical steroids if glaucoma is due to inflammatory trabeculitis

Modified from Pavan-Langston D. Ophthalmic zoster. In: Watson C, Gershon A, eds. Herpes Zoster and Post-herpetic Neuralgia. *2nd ed. Amsterdam: Elsevier Sciences BV; 2001:119–129. Reprinted with permission from Elsevier.*

TABLE 113.4 Management of Herpes Zoster Ophthalmicus (Chronic or Recurrent)

Dendritiform or Immune Keratopathy, Episcleritis, Scleritis, Iritis

See Table 113.3

Tenuous, Hazy Epithelium in Anesthetic Cornea

Early lateral tarsorrhaphy and lubrication with artificial tears and tear ointments
Allow vascularization to progress to aid in healing any ulcer
Topical steroids with caution and only at low doses to minimize any inflammation

Exposure Keratopathy or Corneal Ulceration or Thinning

Lateral tarsorrhaphy
Therapeutic soft contact lens (e.g., Permalens or Kontur)
Tissue adhesive (e.g., Dermabond) for progressive thinning
Conjunctival flap, transplant, or keratoprosthesis

Glaucoma

See Table 113.3

Postherpetic Neuralgia (Drugs Below May Be Used Additively)

Tricyclic antidepressants (e.g., nortriptyline, desipramine, or other tricyclics), 25 mg titrated up to 75 mg qhs or divided dose prn. Caution if patient has cardiac disease.
Gabapentin (Neurontin), 300 mg PO bid starting dose. Efficacy may not be reached until 600 mg bid–qid. Some patients may not respond at all.
Slow-release opioids added if tricyclic antidepressants and/or gabapentin not sufficiently effective; oxycodone (OxyContin), 10–40 mg PO q12h
Capsaicin cream 1–3 times daily to skin as tolerated
Lidocaine skin patches, 12 hours on/12 hours off painful skin area
Frontal and/or nasal nerve block
Trigeminal ganglion ablation contraindicated

Modified from Pavan-Langston D. Ophthalmic zoster. In: Watson C, Gershon A, eds. Herpes Zoster and Post-herpetic Neuralgia. *2nd ed. Amsterdam: Elsevier Sciences BV; 2001:119–129. Reprinted with permission from Elsevier.*

Ganciclovir, a synthetic medication with more broad-spectrum antiviral coverage, has been reported to be effective in treating HSV-, VZV-, and cytomegalovirus-related keratitis. In addition to being just as effective as acyclovir with less ocular toxicity, ganciclovir may also be less likely to promote drug resistance.[142,143] Ganciclovir is being investigated for the treatment of VZV keratitis in a large randomized controlled trial by Northwestern University.[4]

Data in the normal population indicate that the incidence of zoster is much lower in vaccinated healthy children and adults compared with those who have suffered a natural infection.[138] The US Food and Drug Administration (FDA) approval of a live-attenuated VZV vaccine for the immunization of healthy people of all ages who have not had previous varicella, thereby reducing the incidence of varicella and its complications, was hailed as a major step in controlling this disease and is potentially essential to reducing the incidence of zoster.[144] Introduction of a more effective, adjuvanted recombinant protein VZV vaccine for adults over 50 years of age should further reduce the incidence of herpes zoster. One question that continues to be raised is, should every patient with herpes zoster receive antiviral treatment? Gnann and Whitley[145] have recommended that treatment be given to those at high risk of complications: those older than 50 years of age, immunocompromised, having moderately severe to severe pain at presentation, and having a greater degree of skin-surface involvement, and those with HZO. One study of 324 patients compared the effect of antiviral therapy on complications of HZO; the probability of an adverse outcome was 9% in untreated patients and 2% in treated ones.[146]

Sometimes, topical corticosteroids are used as adjuvant therapy to topical antivirals. HEDS I evaluated the effectiveness of corticosteroids (topical prednisolone phosphate) in treating HSV stromal keratitis. The authors reported significantly shorter time to resolution of infection in the prednisolone group, with a median of 26 days for those taking prednisolone and 72 days for those taking placebo ($P < .001$). Visual acuity at 6 months remained similar in both groups.[147]

In case of cytomegalovirus stromal keratitis, the current preferred treatment is oral valganciclovir; however, it has significant side effects, such as aplastic anemia.[148] Valacyclovir has been reported to have better ocular penetration. In addition, its treatment dosage is 1 g three times daily as opposed to acyclovir, which is 400 mg five times a day (800 mg five times a day for VZV). Less frequent dosage often aids in patient compliance.[4,149,150]

Therapy for Ocular Vaccinia

During the previous era of routine smallpox vaccination, the treatment of ocular vaccinia was based predominantly on anecdotal reports of the use of vaccinia immune globulin alone or in combination with idoxuridine or topical interferon. Many of these isolated cases were reported before the availability of more effective topical antivirals, such as trifluridine and vidarabine. In the absence of masked, controlled clinical trials, a meaningful meta-analysis of the literature is not possible. Because of this limitation, some of the current recommendations, which depart from the previous policy designed in the mid-1960s, were made by the CDC after consultation with an outside panel of corneal and external disease and infectious disease specialists.[151] The recommendations are based on principles routinely used in the treatment of other viral diseases of the ocular surface: treat active viral replication with antivirals, followed by cautious use of topical corticosteroids (when appropriate) to prevent inflammatory damage of the cornea and anterior segment. For vaccinia, there is an additional therapeutic agent, intravenous immune globulin. Because ocular vaccinia virus infections are generally self-limited, treatment should be directed toward shortening the course and limiting the severity of the disease. The evaluation and treatment of ocular complications of vaccinia virus should be performed by an ophthalmologist in a timely manner. Intravenous vaccinia immune globulin is not recommended for isolated vaccinia keratitis because of the danger of corneal opacities. ST-246 (tecovirimat [Arestvyr]) has antiviral activity against vaccinia and could prove to be useful for ocular complications of vaccinia (see Chapter 132). Although no topical antiviral is licensed by the FDA for the treatment of ocular vaccinia, topical trifluridine drops or vidarabine ointment can be used off-label for this purpose and either is likely more effective and less toxic than topical idoxuridine or cytosine arabinoside.[152,153] Topical vidarabine may be preferable for use in children because it has been available in an ointment preparation that allows less frequent dosing and is associated with less initial stinging than trifluridine. Vidarabine ointment is currently not commercially available but may be obtained through compounding pharmacists. However, if vidarabine cannot be obtained or the patient would better tolerate drops, trifluridine may be used in children just as it is in ocular herpes simplex. Topical antiviral drugs should be considered for prophylaxis of the conjunctiva and cornea if vaccinia lesions are present on the eyelid, especially if near the lid margin. The use of these drugs for prophylaxis should be balanced against the possible risk of drug toxicity and of introducing virus into the eye by frequent manipulation. Topical trifluridine may possibly have an increased risk of toxicity if used for longer than 14 days. Toxic changes to the ocular surface are almost invariably reversible with discontinuance of the drug.

Therapy for Viral Keratoconjunctivitis

The keratoconjunctivitis associated with EKC (adenoviral mediated) may not require any measures other than artificial tears and possible cycloplegics. There is no effective antiviral for EKC. However, if the condition is associated with significant pain, photophobia, and visual alteration, a course of mild topical corticosteroids, in addition to the cycloplegics, may be beneficial. There have been no definitive trials indicating whether topical steroids alter the typical duration of the disease process.

FUNGAL KERATITIS

Although many genera of molds and yeasts have been identified in fungal keratitis, it is generally much less common than either bacterial or viral keratitis.[154] Although there are great differences based on global geography, fungi have generally been responsible for less than 5% to 10% of corneal infections in most clinical series reported in the United States. Keratitis caused by molds occurs more commonly in areas with a warmer and more humid environment. These fungi are usually inoculated into the cornea by trauma involving plant or vegetable matter. Keratitis caused by *Candida albicans* is acquired from the patient's own flora.

Corticosteroid use has been implicated in altering the cornea's resistance to fungal infection, while certainly potentiating any existing fungal infection. Topical corticosteroid use for medical or surgical ocular conditions (i.e., LASIK), as well as the use of soft contact lenses as a "bandage" for postoperative or damaged corneas, may increase the likelihood of fungal keratitis.

Fungal keratitis remains a diagnostic and therapeutic challenge. Difficulties are related to establishing a clinical diagnosis, isolating the causative agent in the laboratory, and treating the keratitis effectively with topical antifungal agents. Delayed diagnosis is common, primarily because of lack of suspicion; even if the diagnosis is made accurately, management remains a challenge because of the poor corneal penetration and the limited commercial availability of antifungal agents.

Numerous fungi can cause keratitis—*Aspergillus, Curvularia, Paecilomyces, Phialophora, Blastomyces, Sporothrix, Exophiala, Scedosporium,* and *Alternaria*—but *Fusarium* spp. appear to be the most commonly isolated.[155,156] *Nocardia* and *Corynebacterium matruchotii* are rare causes of infectious keratitis but produce a corneal lesion whose appearance is nearly identical to those seen in fungal keratitis. Because the treatment would be quite different, laboratory evaluation is necessary. A number of fungi have been rarely suspected of causing keratitis, but because they are ubiquitous and easily isolated from the environment, their role in true pathogenesis is difficult to ascertain.

The incidence of fungal keratitis varies according to geographic location and ranges from 2% of keratitis cases in New York to 35% in Florida. *Fusarium* spp. are the most common cause of fungal corneal infection in the southern United States (45%–76% of fungal keratitis), whereas *Candida* and *Aspergillus* spp. are more common in northern states. In a large series of fungal keratitis from south Florida, Rosa and colleagues[156] reported that *Fusarium oxysporum* was the most common isolate (37%), followed by, in order of decreasing frequency, *Fusarium solani* (24%), *Candida, Curvularia,* and *Aspergillus* spp.[156]

Clinical Presentation

Patients with fungal keratitis generally have fewer inflammatory signs and symptoms than those with bacterial keratitis. Fungal infections may be mild and indolent, often without suppuration or an ulcerated epithelial surface in the early phases. Molds (most often *Fusarium* or *Aspergillus*) may manifest with gray-white, dry-appearing infiltrates that have a filamentous or feathery edge. The superficial lesions may even appear as strands elevating the corneal surface. Minimal stromal inflammation may be present in a focal or multifocal pattern, along with satellite lesions. Larger lesions or deep invasion may be associated with an endothelial plaque or hypopyon. As the keratitis progresses, extensive suppuration may develop, giving the appearance of a bacterial keratitis. A rapidly increasing hypopyon and anterior chamber membranes may be noted. Such rapidly progressive anterior chamber inflammation may herald fungal extension into the anterior chamber.

Fusarium Keratitis

A number of individuals have contracted *Fusarium* keratitis from contact lens wear, but this number is generally very small. In 2006, the CDC began to receive reports of an increased incidence of contact lens–associated *Fusarium* keratitis. The CDC began an investigation of the *Fusarium* keratitis outbreak, resulting in 130 confirmed cases. More than 60% of people with confirmed *Fusarium* keratitis had used a specific type of contact lens solution; the FDA has recalled that specific solution. Of the 130 confirmed cases of *Fusarium* keratitis, 37 resulted in cornea transplant surgery.[157]

Candida Keratitis

Major predisposing risk factors for keratitis caused by *Candida* spp. are prolonged epithelial ulceration, topical corticosteroid use, recent keratoplasty (corneal transplant), current corticosteroid use, and current use of a "bandage" soft contact lens (i.e., recurrent erosion, persistent

epithelial defect, etc.). *Candida* keratitis is more common in patients with a history of ocular surface disease, previous ocular herpes, exposure keratopathy, and systemic immunosuppression. In contrast to that caused by molds, *Candida* keratitis manifests as an oval epithelial ulceration with an expanding, more sharply demarcated, densely focal suppuration. In this appearance, *Candida* may mimic a gram-positive keratitis, although the inflammatory reaction is generally somewhat less than that seen with bacterial keratitis.

Therapy for Fungal Keratitis: Limited Therapy Options

The development of antifungal preparations has been similar to that for the antivirals in that there are relatively few treatment options for patients. Most agents must be specially formulated, and a number of the oral and parenteral agents cannot be processed into topical solutions because of pH or other solubility difficulties. Natamycin 5% suspension is the only topical ophthalmic antifungal commercially available in the United States. Voriconazole 1% can be prepared in the pharmacy from the intravenous formulation. In a Cochrane review of 12 randomized clinical trials of fungal keratitis, natamycin 5% suspension was superior to voriconazole 1%, although most of the superiority was found in patients with *Fusarium* keratitis. Ten trials were in India, one in Bangladesh, and one in Egypt. There were insufficient data to make conclusions about the relative efficacy of other topical drugs or combinations of topical and oral antifungals.[158] Chlorhexidine gluconate 0.05%, 0.1%, and 0.2% is available in some countries overseas and was considered to be equally effective to natamycin 5% when compared in two randomized trials in Bangladesh.[158,159]

The Mycotic Ulcer Treatment Trial I (MUTT I)[160] compared the efficacy of topical natamycin and topical voriconazole in the treatment of filamentous fungal ulcers. It found that that the group randomized to topical natamycin had an average BSCVA of 1.8 Snellen lines better at 3 months compared to the voriconazole group ($P = .006$). In particular, the *Fusarium* ulcer cases had BSCVA of 4 Snellen lines better when randomized to natamycin compared to voriconazole ($P < .001$). In fact, the Data Safety and Monitoring Committee recommended stopping the trial after enrolling 323 patients because those randomized to topical voriconazole had a statistically significant increase in the rate of corneal perforation or therapeutic penetrating keratoplasty ($P = .009$). Of note, the *Fusarium* ulcers had small scar size at 3 months when treated with natamycin. This was not the case for non-*Fusarium* ulcers. However, on day 6 of the treatment, a higher percentage of the patients were culture positive for fungus in the voriconazole group compared to the natamycin group, regardless of the type of fungus, indicating that natamycin is superior to voriconazole in the treatment of all fungi ($P < .001$). This trial has been corroborated by a second recent randomized clinical trial and the Cochrane review mentioned earlier.[158,161]

Another study reported significantly superior antifungal activity of phenylmercuric nitrate, a the commonly used ophthalmic preservative, in treating fungal keratitis in comparison to natamycin.[162] For *Fusarium* keratitis, a 0.02% solution of polyhexamethylene biguanide was found to be effective as a therapeutic option, especially in cases that were unresponsive to other common antifungal therapies.[163] Proceeding likewise, several studies[164–166] have found nanoparticles of silver more effective than natamycin against the activity of filamentous fungi in vitro.

Topical amphotericin B solution, prepared in a pharmacy, is the recommended treatment for *Candida* keratitis and may be an alternative for *Aspergillus* keratitis. Topical preparations of flucytosine, fluconazole, econazole 2%, miconazole 1%, and itraconazole have been used in clinical and experimental situations. Case reports of using oral itraconazole or oral voriconazole for mold keratitis, in addition to a topical antifungal, have suggested that the combined approach could be considered. Although topical voriconazole in comparison to topical natamycin shows lower efficacy in treating fungal keratitis, it may be effective in oral form as an adjunct to topical voriconazole.[167] The reports of successful treatment with topical voriconazole have invariably used the topical formulation in conjunction with the oral or the intravenous form.[168,169]

Oral fluconazole should be considered for *Candida* keratitis, although experience is limited. Detection of hyphae on wet mounts of corneal scrapings is difficult and mechanical débridement may be necessary because the fungi are often deep within the stroma. The greater sensitivity of calcofluor white staining of wet mounts recommends this technique for corneal scrapings. Penetration of topical agents into the corneal stroma is usually poor, and the fungal infiltration deep within the stroma is frequently unresponsive to such therapy. Cases with progressive disease unresponsive to maximal oral or topical therapy may ultimately require a penetrating keratoplasty to prevent perforation or loss of the globe because of unchecked fungal extension.

Sharma and coworkers performed a study comparing the efficacy of topical voriconazole and topical natamycin with that of intrastromal voriconazole and topical natamycin in patients with recalcitrant fungal keratitis in 2013.[170] Intrastromal injections did not offer any beneficial effect over topical therapy in this study.[170] Intracameral injection of amphotericin with or without hypopyon drainage also offers a potential adjuvant treatment for fungal keratitis.[171–175] Further investigations and evaluations of these adjuvant therapies in well-designed randomized controlled trials is important to assess their benefits.

In line with topical methods of combating fungal keratitis, Homa and colleagues[176] found that the combination of *Cinnamomum zeylanicum* essential oil (whose major component is trans-cinnamaldehyde) and natamycin was effective in inhibiting the fungal activity in *Fusarium* keratitis isolates by the reduction of its cellular metabolism and suppression of its conidia germination.

Another method used for treating keratitis is the administration of riboflavin in combination with corneal collagen cross-linking (CXL).[177–183] A significant decrease in cell morphology of both filamentous fungi and yeast that were exposed to photosensitizing riboflavin and ultraviolet light, respectively, was reported by Kashiwabuchi and coworkers.[177] Labiris and associates reported reepithelialization of corneal epithelium 5 days after CXL treatment, with no relapse (within 12-month follow-up period) in a patient who was suffering from graft ulcer 12 months after a penetrating keratoplasty procedure.[178] Shetty and coworkers[179] also reported the potency of the CXL method in resolving not only fungal but also bacterial keratitis cases that were superficial (not involving deep stromal keratitis and endothelial plaque). Although the occurrence of microbial keratitis after CXL treatment is seldom (0.0017%), moxifloxacin-resistant *S. aureus* can be the potential culprit behind such infection, which must be treated aggressively with fortified antibiotics.[184]

One important consideration to keep in mind while making the diagnosis of fungal keratitis is the morphologic similarity between *Paecilomyces* and *Penicillium* in culture. Sheybani and colleagues[185] reported the drastically different clinical outcomes of two cases of fungal keratitis from *Paecilomyces.* In one case the isolate was misidentified as *Penicillium,* resulting in less than an ideal treatment regimen, with three unsuccessful penetrating keratoplasties prior to a successful one. In the other case, the keratitis cause was correctly identified as *Paecilomyces,* resulting in a successful penetrating keratoplasty from the first attempt.

PARASITIC KERATITIS

Acanthamoeba Keratitis

Acanthamoebae are free-living protozoa ubiquitous in fresh water, well water, brackish water, and soil. These protozoa have been increasingly recognized as a worldwide cause of painful keratitis, resistant to many forms of treatment and ultimately responsible for loss of vision or even loss of the eye.[186] They are resistant to killing by freezing, desiccation, and the chlorination commonly used in municipal water supplies, swimming pools, and hot tubs. They exist as mobile trophozoites or dormant cysts. The vast majority of reported cases of amebic keratitis have been associated with contact lens use,[187,188] although corneal trauma involving contaminated water has been implicated. A significant increase in amebic keratitis was seen when saline tablets were introduced to the general public to enable preparation of homemade saline solutions. A reduction in amebic keratitis was seen after the tablets were taken off the US market; however, a recent outbreak of amebic keratitis showed that such cases still persist.

In 2006, the Illinois Department of Public Health reported an increased incidence of contact lens–associated *Acanthamoeba* keratitis,

dating from 2004. In 2007, the CDC began a retrospective review of culture-proven cases of *Acanthamoeba* keratitis in 22 centers nationwide. The review identified an association of increasing *Acanthamoeba* keratitis and the use of a contact lens solution that was different than that previously associated with the *Fusarium* keratitis outbreak. Although no specific contaminants were found in any of the solutions or the production plant, the manufacturer voluntarily removed this product from the market.[189]

To further investigate the significant increase of *Acanthamoeba* keratitis at the University of Illinois at Chicago, Joslin and coworkers[190] performed a study and reported that the contact lens solution used is independently associated with *Acanthamoeba* keratitis among soft contact lens users. However, it did not explain all cases, suggesting additional factors. In addition, a more recent study described an increase in *Acanthamoeba* keratitis after the outbreak and after the recall of the multipurpose contact lens solution. The study revealed that the yearly number of cases gradually increased from 22 in 1999 to 43 in 2003, with a marked increase beginning in 2004 (93 cases) that continued through 2007 (170 cases; $P < .0001$).[191] A statistically significant decrease in monthly cases reported, from 28 cases in June 2007 (after the recall) to 7 cases in June 2008, was followed by an increase ($P = .0004$) in reported cases thereafter; cases have remained higher than preoutbreak levels. The persistently elevated number of reported cases supports the need to understand the risk factors and environmental exposures associated with *Acanthamoeba* keratitis.[191]

Shoff and colleagues[192] performed a study to determine contact lens solution efficacy against recent clinical and tap water *Acanthamoeba* isolates and to determine whether taurine inclusion increases *Acanthamoeba* survival in contact lens solutions. They found that recent clinical and tap water *Acanthamoeba* strains, representing proven human pathogens and/or household strains, were highly tolerant of contact lens solutions. The Chicago-area tap water strain was most resilient, a concern if tap water is contributing to the *Acanthamoeba* keratitis increase. Results further differentiated resistance among genotype T4 strains, highlighting the importance of multiple strain testing.[192]

Although an ophthalmologist should be immediately consulted to treat any suspected keratitis, an excellent review of *Acanthamoeba* keratitis can be found in Chapter 273.

Clinical Signs and Symptoms With *Acanthamoeba* Keratitis

Patients with amebic keratitis have photophobia and severe pain, often out of proportion to the clinical appearance. A lengthy and worsening course shows little or no response to a variety of antimicrobial agents. Early infection is often limited to the corneal epithelium, manifesting as a diffuse epithelial keratitis, dendritic lesion, or radial keratitis. At this stage, amebic keratitis is often misdiagnosed as herpetic keratitis, and treatment is attempted with antivirals and corticosteroids. Enlarged corneal nerves have been suggested, but perineural inflammation may be a more appropriate descriptor. This radial keratitis/perineuritis is generally not seen with other types of microbial keratitis. A late finding is the "classic" ring infiltrate after progression of the gray-white superficial nonsuppurative infiltrate generally found in the central or paracentral cornea.

Onchocerciasis

The impact of parasitic keratitis is devastating in some tropical regions. Sclerosing keratitis and corneal opacification can be the result of stromal infestation by microfilariae of *Onchocerca volvulus*.[193] The host for this parasite is the black fly found in Africa and certain areas of Central and South America. The female fly deposits her eggs in vegetation and on rocks in streams and rivers. Despite the swiftly flowing cool water, the eggs persist. Onchocerciasis, or "river blindness," is one of the leading causes of blindness throughout the world.[194] The ocular lesions are seen after direct invasion of the anterior segment by the microfilariae. Early in the course of the condition, the patient will complain of tearing, photophobia, and redness. Slit-lamp examination may reveal microfilariae "swimming" in the anterior chamber or slowly moving through the cornea just under the epithelium.[195] The host tolerates the organism surprisingly well; however, a severe inflammatory reaction begins when the microfilariae die in the cornea.[196] Sclerosing keratitis is the eventual blinding complication after many long-lasting infections.

Leishmaniasis

Leishmania keratitis may appear quite similar to that of onchocerciasis.[197] *Leishmania* parasites are obligate intracellular agents transmitted through bites of infected sand flies. Human infection can take many forms, but cutaneous and mucocutaneous varieties cause edema, ulceration, and scarring of the lids or conjunctivae. Corneal involvement may begin as superficial "bumps" (phlyctenules) that progress to abscess formation and possible corneal perforation.

Microsporidia and Trypanosomes

With the increase in infections caused by the human immunodeficiency virus (HIV), microsporidial infections are being more commonly recognized (see Chapter 270). Microsporidia are ubiquitous obligate intracellular parasites now classified as fungi. Except in the immunocompromised patient, they are an unlikely cause of keratitis, generally after traumatic penetration of the stroma. *Vittaforma corneae* (formerly *Nosema corneum*) has been implicated in a few cases in Africa, India, and Japan.[198] *Nosema ocularum* and *Anncaliia* (*Nosema*) *algerae* keratitis have also been reported. The ensuing granulomatous inflammation generally leads to necrotizing thinning and perforation. HIV-positive patients may develop mild conjunctivitis with punctate epithelial keratitis caused by the related microsporidium, *Encephalitozoon cuniculi*.[199] Symptoms may be mild and can easily be mistaken for tear film deficiencies or blepharitis, or both; a high index of suspicion is required in such patients to make a clinical diagnosis of microsporidial keratitis. The tsetse fly can infect humans with the hemoflagellates responsible for African trypanosomiasis, or "sleeping sickness." Ocular effects manifest as unilateral conjunctivitis, periorbital edema, and preauricular lymphadenopathy. IK similar to that seen in syphilitic keratitis has been described.[200]

Therapy for Parasitic Keratitis

Early diagnosis of *Acanthamoeba* infection is the single most *predictive* factor in successful treatment. Most cases are initially diagnosed and treated as herpetic keratitis, further delaying proper treatment and usually allowing treatment with corticosteroids, which is proportionally correlated with a poor outcome. Early diagnosis during the epithelial stage may lead to a good visual outcome after débridement and a 3- to 4-month course of antiamebic therapy. If diagnosis is made after stromal infiltrates appear, the prognosis is more guarded because eradication is quite difficult, often requiring up to a year of antiamebic therapy. Numerous agents have been suggested in treating *Acanthamoeba,* likely indicating that the best therapy is uncertain. Diamidines (propamidine, hexamidine), biguanides (polyhexamethylene biguanide, chlorhexidine), aminoglycosides (neomycin, paromomycin), and imidazoles/triazoles (miconazole, clotrimazole, ketoconazole, itraconazole) have all been used in different combinations, depending on availability. Most of these agents are effective against the free-living trophozoite form of the organism, but none is particularly effective against the cystic stage. In vitro evaluation of topical agents against the cystic form of *Acanthamoeba* found natamycin, povidone-iodine, and acriflavine to have the best activity against this form.[201,202] No agreement exists as to the best combination, but successful outcomes have been achieved using a biguanide with or without a diamidine. Recent reports of success with topical and oral miltefosine are encouraging (see Chapter 273). Controversy exists regarding the use or benefit of corticosteroids because early use may contribute to persistence of viable cysts. Penetrating keratoplasty may be necessary, medically and therapeutically. However, even in a quiet-appearing eye, such surgery has been associated with a recurrence if performed within the first year of the diagnosis, presumably because of persistent cysts. It may be best to complete a full course of antiamebic therapy, followed by a 6-month disease-free course, before considering a penetrating keratoplasty.

The effect of methylene blue–mediated photodynamic therapy (MB-PDT) on *Acanthamoeba* was evaluated by Mito and coworkers[203] in an in vitro study. They reported that MB-PDT suppressed the respiratory activity of trophozoites in a concentration-dependent manner and that MB-PDT had a synergistic effect when used in combination with

polyhexamethylene biguanide or amphotericin B, but not with voriconazole.[203] Further studies are needed before this in vitro approach would be translated to the bedside.

Onchocerciasis was originally treated with diethylcarbamazine, but ivermectin is equally effective and less toxic.[204] Encephalitozoon conjunctivitis has responded to albendazole 400 mg PO bid (see Chapter 270), suggesting that the drug should be considered for keratitis. Experience with other agents has been discouraging. Penetrating keratoplasty has been used as a last resort.

It is important to consider the possibility of coinfection with multiple agents, especially in cases with contact lens–related keratitis.[204–207] In a study by Sharma and associates,[205] *Acanthamoeba* and *P. aeruginosa* were both found to be causing keratitis when a 20-year-old woman presented to the emergency department of their hospital with a 4-day history of progressively increasing pain, redness, photophobia, mucopurulent discharge, and decrease of vision in her right eye. Similarly, in a retrospective study, Lim and colleagues[206] identified the size of the corneal infiltrate, the prolonged course of the disease, and the decreased antibiotic sensitivity as the indicators of coinfection with multiple agents, which they term *polymicrobial keratitis.*

NOVEL THERAPEUTICS

Therapies continue to evolve for the treatment and prevention of microbial keratitis, specifically to address the serious risks of drug-resistant bacterial infections.

Duan and coworkers[208] modified emodin to synthesize haloemodin, which they used to cure *S. aureus*–induced keratitis in a rabbit model. They found that haloemodin shows antibacterial activity against gram-positive bacteria by exerting an inhibitory activity on bacterial DNA gyrase and topoisomerase I, without showing any inhibitory effect on human topoisomerases. Kolar and colleagues[209] derived a frog skin peptide called esculentin-1a(1-21)NH_2, which was tested in vitro and in vivo in a murine model of *P. aeruginosa* keratitis. Inflammatory cell recruitment was reduced by half in the treated group compared to the control mice, and no toxicity was shown in human epithelial cells up to 50 μM (MIC between 2 and 16 μM), showing promise in the development of novel topical drugs against *P. aeruginosa*. Working with the same frog skin–derived peptide and esculentin-1a and homologous esculentin-1b, Mangoni and associates[210]further found the peptide's membranolytic activity on both free-living and biofilms of *C. albicans.*

In addition, lipid-based ophthalmic drug delivery has been investigated. Carrier systems such as liposomes, lipid microsphere and lipid microtubules, solid lipid nanoparticles, and lipid suspensions and emulsions have been used to deliver drugs for the treatment of various ocular surface diseases. Ustündağ-Okur and coworkers[211] reported one such system in which they delivered oxofloxacin via nanoparticles of lipid carriers modified with chitosan oligosaccharide lactate to treat bacterial keratitis. The addition of chitosan oligosaccharide lactate prolonging the residence time of the drug.

Researchers from Australia found that N-glycan in tears bound to *P. aeruginosa* (especially the cytotoxic strain compared to the invasive strain). Binding allowed the tears to wash away the microbe.[212]

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The complete reference list is available online at Expert Consult.

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114 Endophthalmitis

Marlene L. Durand

SHORT VIEW SUMMARY

Definition

- Endophthalmitis is a bacterial or fungal infection inside the eye, involving the vitreous and/or aqueous. It is either exogenous, in which infection is introduced from the outside in, or endogenous, in which the eye is seeded from the bloodstream.

Clinical Manifestations

- Decreased vision and eye pain are usually present. Hypopyon (layer of white blood cells in aqueous humor) is commonly seen. No fever or leukocytosis is present in exogenous cases and may also be absent in endogenous cases.

Categories and Microbiology
(see Table 114.1)

- *Acute postcataract endophthalmitis.* Incidence is approximately 0.1% of cataract surgeries, with onset within 1 week postoperatively in 75%. The most common etiology is contamination of the aqueous from ocular surface flora. Gram-positive cocci cause 95% of cases, with coagulase-negative staphylococci the major pathogens (70% of all cases).
- *Chronic postcataract endophthalmitis.* Rare, this category presents as a low-grade inflammation in the aqueous postoperatively that persists for months. It may respond to topical corticosteroids initially but recurs as the drug dosage is tapered. The cause is *Cutibacterium (Propionibacterium) acnes* in most cases.
- *Postinjection endophthalmitis.* Incidence is approximately 0.1% after each intravitreal injection of an anti–vascular endothelial growth factor agent (treatment of wet macular degeneration). Injections are typically given once monthly. Major pathogens are coagulase-negative staphylococci and streptococci (25% of cases), the latter usually causing severe endophthalmitis.
- *Bleb-related endophthalmitis.* A filtering bleb is a "bleb" of conjunctiva overlying a surgically created defect in the sclera. Creation of a filtering bleb is one treatment for medically refractory glaucoma. Endophthalmitis typically occurs suddenly, months to years postoperatively; the incidence is approximately 0.5% per patient-year but may be much higher in leaking blebs. Infection is often fulminant because streptococci, enterococci, and *Haemophilus influenzae* are major pathogens.
- *Posttraumatic endophthalmitis.* Incidence is 0.9% to 10% after penetrating eye trauma ("open globe"), with the lower incidence reported using a protocol that includes 48 hours of prophylactic antibiotics. Coagulase-negative staphylococci and *Bacillus cereus* are major pathogens; *B. cereus* is most feared and causes fulminant infection.
- *Keratitis-related endophthalmitis.* Occurs when infection of the cornea extends into the aqueous. Molds are the most common etiology.
- *Endogenous bacterial endophthalmitis.* Common sources include endocarditis (*Staphylococcus aureus* and streptococci are major pathogens), intraabdominal abscess (e.g., liver abscess due to *Klebsiella pneumoniae* in East Asian nations), urinary tract infection, transient bacteremia (e.g., endoscopy, intravenous drug abuse).
- Candida *endophthalmitis.* This category is usually endogenous. Chorioretinitis, the earliest manifestation, is often asymptomatic. Chorioretinitis usually responds to systemic antifungal treatment alone, but cases with endophthalmitis (marked vitreous inflammation) also require intravitreal antifungal injection and often vitrectomy.
- *Mold endophthalmitis.* Exogenous cases occur after eye surgery, eye trauma, or as an extension of keratomycosis (fungal corneal infection), whereas endogenous cases most often occur in injection drug users or severely immunocompromised hosts. *Aspergillus* and *Fusarium* are the most common pathogens.

Diagnosis

- Exogenous cases, and some endogenous cases, require vitreous aspirate or vitrectomy for culture (aqueous may also be cultured). Endogenous cases with positive blood cultures are usually presumed to be due to the same organism.

Therapy

- Intravitreal antibiotics and often vitrectomy (surgical débridement of the vitreous) are required. Systemic antibiotics alone are not effective in treating endophthalmitis, except in cases of *Candida* chorioretinitis.

Endophthalmitis refers to bacterial or fungal infection involving the vitreous and/or aqueous humors. Most cases of endophthalmitis are caused by bacteria and present acutely. Acute endophthalmitis is a medical emergency because delayed or inadequate therapy may result in irreversible vision loss. Endophthalmitis may be either exogenous, in which organisms are introduced directly into the eye from an external source, or endogenous, in which the eye is seeded during bacteremia or fungemia. Most cases are exogenous and occur after eye surgery, intraocular injections (e.g., given for treatment of macular degeneration), eye trauma, extension of corneal infection (keratitis), or from a glaucoma filtering bleb.[1] Postcataract endophthalmitis is the most common type worldwide, but postinjection or posttraumatic endophthalmitis may be more common at some centers.[2]

In exogenous endophthalmitis, the infection is confined to the eye, and there are rarely any systemic symptoms. In endogenous endophthalmitis patients may have prominent symptoms of the underlying systemic infection (e.g., endocarditis).

CATEGORIES

It is useful to further classify endophthalmitis into several categories (Table 114.1). The presentation and typical pathogens vary by category, but treatment almost always requires the intraocular injection of antibiotics and, often, vitrectomy.

Acute Postoperative Endophthalmitis

Endophthalmitis may occur after any eye surgery, but most postoperative endophthalmitis cases occur after cataract surgery. Cataract surgery is one of the most common surgeries performed worldwide, with more than 3.5 million cataract surgeries performed annually in the United States alone. The cataract, or opacified lens, is most often broken up

TABLE 114.1 Endophthalmitis Categories and the Most Common Pathogens in Each

CATEGORY	COMMON PATHOGENS
Acute postoperative	Coagulase-negative staphylococci
Chronic postcataract	*Propionibacterium acnes*
Postinjection	Viridans streptococci, coagulase-negative staphylococci
Bleb-related	Streptococci, *Haemophilus influenzae*
Posttraumatic	*Bacillus cereus*
Keratitis related	Molds (e.g., *Fusarium*)
Endogenous	*Staphylococcus aureus,* streptococci, gram-negative bacilli
Fungal	*Candida, Aspergillus, Fusarium*

and removed by phacoemulsification, a technique using ultrasound. During cataract surgery, an incision is made through the sclera or cornea and then through the anterior lens capsule to remove the lens. An attempt is made to leave the posterior lens capsule intact. In most cases an artificial intraocular lens (IOL) is placed in the residual capsular bag. The incidence of postcataract endophthalmitis is approximately 0.1% in the United States, based on Medicare data 2010–14.[3] Other countries report rates from 0.03% to 0.2%.[4–6]

The pathogens causing postcataract endophthalmitis usually come from the patient's own eyelid or conjunctival flora, which may contaminate the aqueous during surgery.[7,8,9] The widely used "clear cornea" incision (incision through the cornea), which is sutureless and self-sealing, may increase the risk of endophthalmitis compared with the older "scleral tunnel" incision.[10,11] Clear cornea incisions may gape intermittently in the early postoperative period, leading to potential contamination.[12,13] Recent cataract surgical techniques have included femtosecond laser-assisted cataract surgery, but comparisons with standard phacoemulsification cataract surgery have not demonstrated a difference in postoperative complications.[14]

The vitreous is more susceptible to infection than the aqueous, and the risk for postcataract endophthalmitis is at least sixfold higher if the posterior lens capsule is inadvertently broken during surgery, thereby establishing a communication with the vitreous.[15,16] Silicone rather than acrylic IOLs also increase the risk for endophthalmitis.

Symptoms of endophthalmitis occur within 1 week of surgery in 75% of patients and include eye pain (74%), redness (82%), and decreased vision (94%).[16] The patient often has no symptoms for several days, and then symptoms develop rapidly within 24 hours. The pain is often not severe, and patients feel otherwise well. Signs of systemic illness are absent: There is no fever, and the white blood cell count is normal in two-thirds of patients and only mildly elevated in the rest. The physical examination is unremarkable except for the involved eye, which is usually injected and has a hypopyon (Fig. 114.1). The hypopyon is a layer of white blood cells in the anterior chamber. Slit-lamp examination reveals white blood cells in the aqueous and vitreous. Inflammation may be so severe that it obscures the funduscopic view of the retina.

In temperate climates nearly all postcataract endophthalmitis cases are due to bacteria, and 95% are due to gram-positive cocci. Coagulase-negative staphylococci are the major pathogens, causing 70% of culture-positive cases, regardless of whether a scleral tunnel or clear cornea incision was used for the surgery.[16,17] *Staphylococcus aureus* (10%), streptococci (9%), other gram-positive cocci (5%), and gram-negative bacilli (6%) account for the remaining cases. Streptococci (e.g. viridans streptococci, *Streptococcus pneumoniae,* and β-hemolytic streptococci) are associated with a particularly poor outcome. Thirty percent of patients with clinical evidence of endophthalmitis have negative or equivocal vitreous cultures.[16] In tropical countries, such as India, fungi typically cause 10% to 15% of postoperative endophthalmitis cases.[18]

Chronic Postcataract Endophthalmitis

Chronic postcataract endophthalmitis, also termed *chronic pseudophakic endophthalmitis* in reference to the IOL, is a rare, indolent infection that is almost always due to *Cutibacterium (Propionibacterium) acnes.*

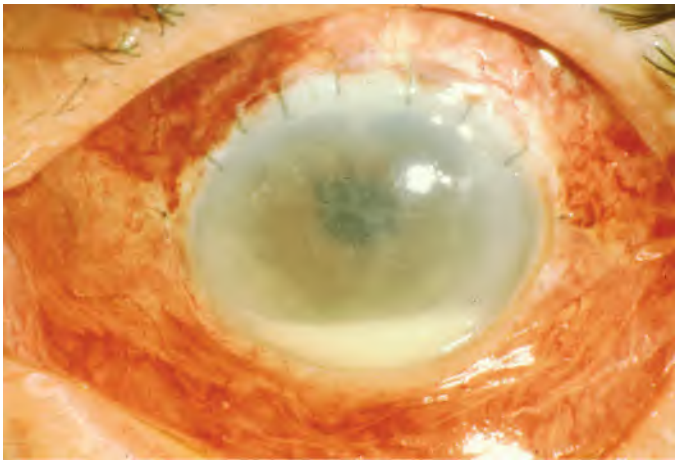

FIG. 114.1 Endophthalmitis. Eye with endophthalmitis, illustrating a hypopyon. *(Courtesy Donald J. D'Amico.)*

A few cases have been caused by coagulase-negative staphylococci, diphtheroids, and fungi. Patients present with a persistent decrease in vision in the involved eye, and half also have eye pain, which is usually mild. On slit-lamp examination there are white blood cells in the anterior chamber and usually also in the anterior vitreous. A small hypopyon is present in half of patients, and in nearly all patients there is a white plaque in the residual posterior lens capsule. Patients often are misdiagnosed as having anterior uveitis and may be treated for months with topical corticosteroids, producing a waxing and waning course of intraocular inflammation. Diagnosis may be difficult because aqueous or vitreous cultures are frequently negative, even in cases in which electron microscopy of the removed artificial lens or lens capsule shows bacteria.[19] Polymerase chain reaction (PCR) testing of intraocular samples or of the explanted IOL may be helpful.[20] Biopsy of the posterior lens capsule, including the white plaque, is most likely to yield positive cultures due to *P. acnes*. Treatment of chronic *P. acnes* endophthalmitis usually requires surgical removal of the infected lens capsule and IOL, in addition to intraocular antibiotics, as relapse rates can be very high (70%) with intravitreal antibiotics alone.[21,22]

Postinjection Endophthalmitis

Neovascular, or "wet," macular degeneration accounts for approximately 10% of age-related macular degeneration (AMD) cases. In 2004 the US Food and Drug Administration approved the first anti–vascular endothelial growth factor (anti-VEGF) agent for treating wet AMD, and the annual number of intravitreal injections in the United States rapidly increased. A Medicare study found that 2.4 million intravitreal injections were given in 2012 alone.[23] Intravitreal injections of anti-VEGF agents, such as bevacizumab, ranibizumab, aflibercept, or pegaptanib, are usually repeated monthly, over many months. Each injection carries a risk of endophthalmitis, reported to be between 0.04% to 0.09%.[24,25] Intravitreal anti-VEGF agents may also be given for other indications, such as diabetic retinopathy. Symptoms of endophthalmitis usually develop within 1 week after injection and include eye pain and decreased vision. A hypopyon is found in about 80% of patients. As with postcataract endophthalmitis, gram-positive cocci cause 95% of cases, but viridans streptococci cause a much higher percentage of postinjection cases (25%) than postcataract endophthalmitis cases (9%). Patients with streptococcal endophthalmitis have a poor visual prognosis.[26]

Bleb-Related Endophthalmitis

A filtering bleb is a defect in the sclera, covered only by conjunctiva, that is surgically created to control glaucoma refractory to medical treatment. The bleb allows excess aqueous to filter out of the eye and into the systemic circulation. Because the only barrier to the aqueous humor at the site of the bleb is the thin conjunctiva, acute endophthalmitis may occur at any time, particularly if the eye becomes colonized by virulent bacteria. Bleb-related endophthalmitis usually occurs abruptly, months to years after bleb surgery. The risk of endophthalmitis in one

series was 1.3% per patient-year[27], whereas a large multicenter study from Japan found a 5-year risk of only 1%.[28] The Japanese study found that a leaking bleb increased the risk fivefold. Bleb-related endophthalmitis is typically fulminant. Patients complain of sudden onset of eye pain and decreased vision. On examination the patient has an injected eye, a hypopyon, and often a purulent bleb.[29] The major pathogens include streptococci (36%), coagulase-negative staphylococci (18%), *S. aureus* (11%), enterococci (9%), and *Haemophilus influenzae* (5%).[30]

Posttraumatic Endophthalmitis

Posttraumatic endophthalmitis develops in 0.9% to 10% of eyes that have sustained penetrating trauma.[31,32,33] Endophthalmitis is most likely to follow a lacerating injury with a metal object, whereas glass laceration injuries and blunt trauma rarely lead to endophthalmitis. Other risk factors include lens disruption, retained intraocular foreign bodies, and delay in primary closure of greater than 24 hours.[34] A computed tomography (CT) scan can be helpful in finding metallic intraocular foreign bodies, and magnetic resonance imaging (MRI) is helpful in detecting nonmetallic foreign bodies; note that a CT scan should be performed before MRI to ensure there is no metallic foreign body present at the time of MRI. *Bacillus* spp. (often *Bacillus cereus*) and coagulase-negative staphylococci are the major causes of posttraumatic endophthalmitis. Whereas eyes with endophthalmitis due to coagulase-negative staphylococci often have a good visual outcome, those with *Bacillus* endophthalmitis usually lose all useful vision.[35] Rare cases of successful therapy have been described.[36] Onset of symptoms in 12 to 24 hours after trauma, marked intraocular inflammation, and a ring corneal infiltrate are characteristic of this infection. Other causes of posttraumatic endophthalmitis include streptococci, gram-negative bacilli such as *Klebsiella* and *Pseudomonas,* and molds.[34] Unlike bacterial cases, posttraumatic endophthalmitis due to molds usually has a subacute presentation.

Keratitis-Related Endophthalmitis

An infection of the cornea, or keratitis, usually starts at the corneal surface. In severe cases of bacterial or, more often, fungal keratitis, the infection may extend through the full thickness of the cornea and into the aqueous, thereby causing endophthalmitis. The infection may continue to progress and involve the vitreous. Keratitis-related endophthalmitis is usually rare and comprises less than 1% of cases of endophthalmitis treated at most centers. Some centers, particularly from hot or tropical climates, report a higher incidence. A referral center in Iran found that 8% of all endophthalmitis cases were keratitis-related, with *Pseudomonas* being the most common virulent pathogen isolated. Coagulase-negative staphylococci were isolated more often, but these may have been ocular surface contaminants.[37] Molds cause the majority of keratitis-related endophthalmitis cases worldwide, and molds accounted for over half of such cases at a center in Florida.[38] Exogenous mold endophthalmitis is discussed as follows.

Endogenous Bacterial Endophthalmitis

Endogenous bacterial endophthalmitis is rare and results from bacteremic seeding of the eye. Only 0.04% of hospitalized patients with bacteremia have endophthalmitis.[39] Usually a significant focus of bacteremia is identified, such as endocarditis or an intraabdominal abscess, but transient bacteremia rarely may cause endophthalmitis. Endocarditis was the source in nearly 40% of cases in one United States series of 28 patients, whereas 1 patient developed endophthalmitis 2 days after upper gastrointestinal (GI) endoscopy, presumably from transient bacteremia.[40] Patients who are injection drug users also are at risk for endophthalmitis from transient bacteremia. GI or hepatic abscesses, urinary tract infections, meningitis, and infected indwelling catheters are other sources of bacteremia in endogenous endophthalmitis case series.[40,41,42] In Taiwan, Singapore, and other East Asian nations, pyogenic liver abscess due to *Klebsiella pneumoniae* is prevalent[43] and may be complicated by endogenous endophthalmitis in almost 10% of patients.[44]

The bacteria involved in endogenous endophthalmitis (e.g., *S. aureus,* streptococci, gram-negative bacilli) typically cause acute inflammation, and most patients present with eye pain and acute decrease in vision. These may be their only complaints, and the source of bacteremia may not be apparent initially. In one series half of the patients presented to an ophthalmologist.[40] In a series of 27 patients with fungal or bacterial endogenous endophthalmitis, less than 20% of patients had fever on presentation, and greater than 40% had an unremarkable general physical examination.[42] A delay in diagnosis is common, but endophthalmitis should be considered in any patient who presents with acute vitritis and hypopyon. Patients with known endocarditis should be monitored for new visual complaints and examined by an ophthalmologist promptly if these develop.

Diagnosis usually is established by culture of vitreous samples or by blood cultures in patients with endophthalmitis whose vitreous cultures fail to grow. Blood cultures are positive in approximately three-fourths of patients tested, as are vitreous cultures.[40] In North America and Europe, streptococci (*S. pneumoniae, Streptococcus anginosus* group, and group A and group B streptococci) cause 30% to 50% of cases, and *S. aureus* causes about 25% of cases; gram-negative bacilli (e.g., *Escherichia coli, Klebsiella, Serratia*) cause only one-third of cases.[40,42] In Asia gram-negative bacilli (e.g., *Klebsiella, E. coli*) cause the majority of cases, with *K. pneumoniae* accounting for 60% of cases in one study.[45] In Taiwan a syndrome of *Klebsiella* liver abscess and endophthalmitis occurring primarily in diabetic patients has been well described[46] and appears to be associated with a strain of *K. pneumoniae* exhibiting a hypermucoviscosity phenotype.[47]

Mycobacterial Endophthalmitis

Endophthalmitis caused by nontuberculous mycobacteria (NTM) is very rare, with only 19 cases seen over a 24-year period at a major eye referral hospital in Florida.[48] Nearly all cases in this series occurred after eye surgery, with cataract or glaucoma-device implant surgery accounting for two-thirds of cases; 2 cases occurred after intravitreal injections. Rare cases related to extension of keratitis have also been described.[49] Rapidly growing NTMs such as *Mycobacterium chelonae, Mycobacterium abscessus*, and *Mycobacterium fortuitum* account for the majority of cases. In most cases the endophthalmitis presents as a subacute or chronic inflammation. Treatment is difficult, and relapses are common. Hematogenously disseminated tuberculosis can involve the eye and usually presents as a uveitis, as discussed in Chapter 115.[50]

Fungal Endophthalmitis

Fungal endophthalmitis cases may be divided into two major categories by incidence and response to therapy: *Candida* endophthalmitis and mold endophthalmitis. In industrialized nations and colder climates *Candida* endophthalmitis is more common than mold endophthalmitis, whereas the reverse is true in tropical countries. *Candida* endophthalmitis is most often endogenous and usually responds well to treatment, whereas mold endophthalmitis is almost always exogenous and successful therapy is uncommon. Endophthalmitis due to *Cryptococcus* or the dimorphic fungi, *Histoplasma* and *Coccidioides,* is rare and almost always a result of disseminated disease.

Endogenous *Candida* Endophthalmitis

In the literature on endogenous *Candida* endophthalmitis the term is used variably. In some reports it is used to describe both chorioretinitis and "endophthalmitis" (i.e., infection with significant vitritis), whereas in other reports it is used only for those cases with significant vitritis (the usual meaning of endophthalmitis). A better term is ocular candidiasis, which encompasses the spectrum of intraocular infection from chorioretinitis to endophthalmitis. To avoid confusion, we will reserve "endophthalmitis" for those cases with significant vitritis, and the degree of vitritis will be described. Ophthalmologists grade the degree of vitreous inflammation on a scale of 1 to 4, with 1+ white blood cells considered mild vitritis, and 4+ cells severe vitritis. Determining the degree of vitreous inflammation is important. Ocular candidiasis with moderate-to-severe vitritis (i.e., endophthalmitis) requires intravitreal injection of amphotericin or voriconazole and usually vitrectomy, in addition to systemic therapy. In contrast, chorioretinitis with minimal or no vitritis usually resolves with systemic therapy alone. Visual outcome also depends on the initial degree of vitreous involvement.[49,51]

Candidemic seeding of the eye starts in the highly vascular choroid, so chorioretinitis is the initial manifestation seen in most prospective

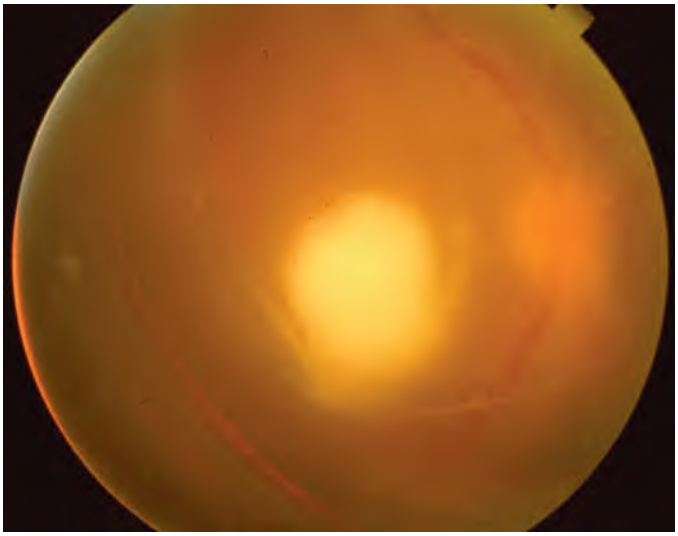

FIG. 114.2 *Candida* endophthalmitis. *Candida* endophthalmitis, with cloudy vitreous and central vitreal "fluff ball."

trials of candidemia. In chorioretinitis there are typically several white chorioretinal lesions but a clear vitreous. As infection progresses there is significant vitritis, and examination reveals a cloudy vitreous that often contains inflammatory "fluff balls" (Fig. 114.2). Chorioretinitis is much more common than endophthalmitis, and chorioretinitis often is asymptomatic. Two trials of candidemic patients found chorioretinitis in 9% to 14% but endophthalmitis in 0% to 1.6%.[52,53] Undiagnosed and untreated chorioretinitis may progress to endophthalmitis, and patients with the latter usually present with a gradual and painless decrease in vision. This presentation is common in outpatients who have had transient, usually asymptomatic, candidemia.

Risk factors for endogenous *Candida* endophthalmitis in hospitalized patients include indwelling central venous catheters, total parenteral nutrition, neutropenia, recent GI surgery or GI perforation, broad-spectrum antibiotic use, and immunosuppression, including glucocorticoid use.[54,55] The major risk factors in outpatients are indwelling central venous catheters (or recent history of such a catheter) and illicit injection drug use. Illicit intravenous drug use (IVDU) is the most common risk factor in some recent studies and accounted for 70% of cases of fungal endophthalmitis from 2001–07 in a study from Australia.[56] A recent series from a Massachusetts eye hospital found that IVDU accounted for 44% of all endogenous endophthalmitis cases diagnosed from 2006–14, and *Candida* species caused 75% of the culture-positive IVDU-related cases.[57] Rare cases of endogenous endophthalmitis in outpatients have occurred after urinary tract procedures, such as ureterolithotomy.[58]

Outpatients who present with endogenous *Candida* endophthalmitis often have a subacute presentation (i.e., 2 weeks of progressive vision loss) and may be misdiagnosed as having uveitis, especially if a history of an indwelling central venous catheter in the previous months or injection drug use is not elicited. Such patients do not usually show other signs of systemic infection, and blood cultures are usually negative because candidemia was transient and occurred days or weeks earlier. Only 6% of IVDU-related *Candida* endophthalmitis cases had positive blood cultures in one series.[57] There is often a substantial delay in diagnosis, and such a delay may lead to permanent vision loss. Although vitreous aspirate alone may yield the diagnosis in some cases, this is often nondiagnostic, and a vitrectomy for culture is usually necessary to make the diagnosis.

Exogenous *Candida* Endophthalmitis

Exogenous cases are uncommon but may develop after eye surgery, eye trauma, or keratitis.[59] Initially, only the aqueous may have inflammation, and then the infection may extend into the vitreous. Rarely, endophthalmitis may develop after corneal transplantation (postkeratoplasty endophthalmitis). The overall incidence of postkeratoplasty endophthalmitis is 0.03% in the United States, and two-thirds of these cases are due to *Candida* (one-third to bacteria).[60] Contaminated donor corneas are usually the source, and culture of the unused donor corneal rim at time of surgery may be helpful. A rim culture that grows *Candida* spp. predicts a 3% chance of developing *Candida* endophthalmitis.[61] Awareness of this increased risk may allow earlier detection and treatment of postkeratoplasty fungal endophthalmitis. Contamination of donor corneas with *Candida* may develop during storage in standard media that contain broad-spectrum antibacterial antibiotics but typically no antifungal agents.[62]

Mold Endophthalmitis

Endophthalmitis due to molds is rare in Western countries. In the United States it is most common in tropical areas, such as Florida, where 6% of 278 endophthalmitis cases treated between 1996 and 2001 were due to *Aspergillus* and other molds.[63] In tropical countries, such as India, fungal endophthalmitis is a significant problem. Molds accounted for 22% of 124 postcataract endophthalmitis cases in northern India[64] and 21% of 170 postoperative endophthalmitis cases in southern India.[65]

Mold endophthalmitis is usually exogenous, with most cases occurring after eye surgery, after penetrating eye trauma, or as an extension of fungal keratitis (keratomycosis).[59]

Postoperative mold endophthalmitis usually presents within days to weeks of eye surgery. Patients complain of eye pain and decreased vision. The surgical corneal or scleral incision may appear normal or may show evidence of wound involvement.[66] Extensive eye involvement (cornea, anterior segment, vitreous) and early presentation (37% within 1 week) characterized postcataract fungal endophthalmitis in one series from India.[67] Posttraumatic mold endophthalmitis also may present relatively quickly; in a series from India the average time to presentation after eye trauma was 7 days.[68] In endophthalmitis due to keratomycosis the diagnosis is made when there is evidence of extension of the corneal infection into the aqueous. On slit-lamp examination the fungal keratitis extends through the full thickness of the cornea, and there is significant inflammation in the aqueous. Sometimes, frondlike projections may be seen extending from the back of the cornea into the aqueous. Both corneal trauma and contact lens wear are risk factors for keratomycosis-associated endophthalmitis.

Endogenous mold endophthalmitis has been reported primarily in IV drug abusers or immunocompromised patients. The latter include organ transplant patients and patients with hematologic malignancies.[69,70] Most of these immunocompromised patients have a focus of fungal infection elsewhere, usually the lungs.[69,70]

Aspergillus is the most common cause of mold endophthalmitis, causing 50% to 90% of cases.[65,68] *Fusarium* is another common cause of mold endophthalmitis, and most cases result from *Fusarium* keratitis. Several cases occurred after a nationwide outbreak of *Fusarium* keratitis, from 2004–06, associated with a contact lens cleaning solution.[71,72] In this outbreak 6% of cases developed endophthalmitis.[71,73]

DIAGNOSIS

Endophthalmitis must be suspected clinically based on the appearance of the eye in a patient with an appropriate risk factor for endophthalmitis. The diagnosis usually is confirmed by culture of the vitreous or, less often, the aqueous. The endophthalmitis patient is afebrile and has no signs of systemic infection except in two situations: endogenous endophthalmitis, in which there is another focus of infection, and panophthalmitis, in which infection has spread from the globe to the orbit. Panophthalmitis is rare, caused by virulent pathogens (e.g., *S. pneumoniae*), and characterized by signs of endophthalmitis plus orbital cellulitis (marked edema and erythema of the eyelids, proptosis, and limitation of extraocular movements). Except for cases of endogenous endophthalmitis and panophthalmitis, blood cultures are negative, and the white blood cell count is normal or only slightly elevated.

Radiologic studies are rarely helpful in acute endophthalmitis and, except for a B scan ("brightness" scan), are not warranted before diagnostic vitreous sampling and therapy. The B-scan is an ultrasound of the globe of the eye. It can confirm the presence of vitreous inflammation or show a retinal detachment in cases in which the vitreous cannot be seen (e.g., dense cataract or extensive aqueous inflammation). The normal vitreous is echo free, whereas multiple vitreous echoes are

present when there is vitritis. The diagnosis of endophthalmitis is usually made by culturing a sample of the vitreous. The aqueous also may be cultured and is aspirated easily in the ophthalmologist's office, but aqueous cultures rarely add additional information. In one large study in which aqueous and vitreous samples were obtained, aqueous samples yielded the only positive cultures in just 4% of cases.[74] The vitreous may be sampled, either by needle aspirate or by vitrectomy (Fig. 114.3). A needle aspirate yields 0.2 to 0.3 mL of vitreous and may be performed in the ophthalmologist's office using a 27-gauge needle and syringe. A vitrectomy is performed in the operating room using a 20-gauge vitrector attached via tubing to a sterile collection bag or canister; more recently, a narrower 23-gauge vitrector has been used with success.[75] Suction is provided by a Venturi-aspiration vitrectomy machine. The vitrector simultaneously cuts and suctions the gel-like vitreous. A separate cannula placed in the vitreous provides continuous infusion of balanced salt solution to maintain eye turgor during the procedure, and this dilutes the vitreous sample. The result is a collection canister or bag containing dilute (20–100 mL) vitreous "washings." An undiluted vitreous sample called a *biopsy specimen* also may be obtained with the vitrector at the start of the case by attaching a syringe via three-way stopcock.

Gram stains of vitreous samples are positive for organisms in approximately half of bacterial endophthalmitis cases. Positive stains are highly predictive of positive cultures, but negative stains have little predictive value.[74] A unique feature of Gram stains of aqueous or vitreous samples from an inflamed eye is the pigment granule.[1] Pigment granules are most likely melanin released from the iris or retinal pigment epithelium. They appear football shaped or spherical, and the latter may be mistaken for gram-positive cocci. Their true identity is evident when the microscope focus is varied because pigment granules are highly refractile and appear copper colored with focus modulation, whereas bacteria do not (Fig. 114.4).

Vitreous washings are more likely to yield positive cultures (75%–90% of cases) than are vitreous aspirates or biopsy specimens (50%–75% of cases).[16,76] Although aspirate or biopsy samples may be cultured directly on various media (blood agar, chocolate agar, broth, and Sabouraud media), vitreous washings first should be filtered through a 0.45-μm filter. The filter paper is sterilely cut into fourths and placed onto agar plates. Before this filtration procedure, a 3-mL sample of the washings should be aspirated from the vitrectomy canister and centrifuged to produce a pellet that may be smeared on a slide for Gram stain. A negative culture does not exclude endophthalmitis, and up to one-third of clinically diagnosed endophthalmitis cases are culture negative. The rate of false-positive cultures is unknown but is reduced if positive cultures are counted as those with moderate-to-abundant growth or growth on two media. In a study of 36 patients undergoing vitrectomy for noninfectious indications, one-fifth of cultures were positive, but organisms (mostly coagulase-negative staphylococci) grew on only one medium, indicative of a low inoculum.[77]

Molecular diagnostic techniques, such as PCR assay, have been used both to diagnose unusual pathogens (e.g., *Neisseria meningitidis*,[78] *Bartonella henselae*)[79] and to improve pathogen detection.[80] Some caution must be exercised if bacteria that usually colonize the ocular surface, such as coagulase-negative staphylococci, are detected: These may represent only ocular surface contaminants rather than intraocular pathogens. False-positive rates by PCR assay of 5% to 14% have been reported in uninfected eyes.[81,82] However, this assay does appear promising. In a study from Brazil of 11 patients with postcataract endophthalmitis, PCR assay was more often positive than culture (91% vs. 75%).[83] In the control group none of 12 vitreous cultures was positive, although 2 of 50 aqueous cultures were. In a study from France of 100 postcataract cases, PCR assay was no more sensitive than culture of initial intraocular samples, before any intravitreal antibiotics were given.[84] However, PCR assay was much more sensitive (70% vs. 9%) in subsequent vitreous

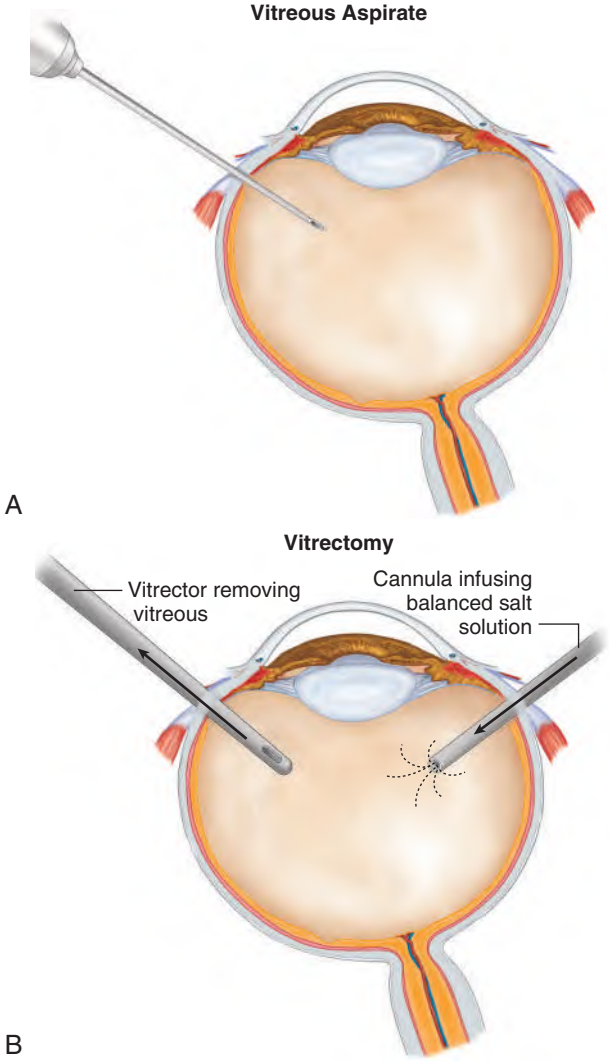

FIG. 114.3 Vitreous aspirate and vitrectomy. Diagram of vitreous aspirate (A) and vitrectomy (B).

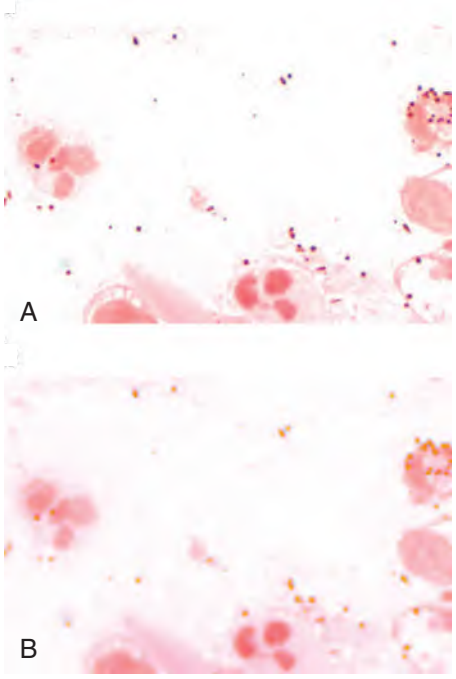

FIG. 114.4 Pigment granules, as seen on a gram stain of intraocular fluid in a case of endophthalmitis. Pigment granules appear (A) purple on Gram stain, but (B) coppery (hyperrefractile) if the fine focus knob of the microscope is rotated back and forth. *(From Durand ML. Bacterial and fungal endophthalmitis.* Clin Microbiol Rev, *2017;30:597–613.)*

cultures, reflecting either false-negative cultures due to the persistence of the intravitreal antibiotics in the vitreous sample or false-positive PCR results due to detection of dead pathogens.

THERAPY

Acute Bacterial Endophthalmitis

Acute bacterial endophthalmitis is a medical emergency because delay in giving appropriate therapy may lead to irreversible loss of vision. The most important component of treatment is direct injection of antibiotics into the vitreous by the ophthalmologist. This can be done in an office procedure room after a needle aspirate of the vitreous was sent for culture (called *tap and inject*) or at the conclusion of a vitreous débridement procedure (vitrectomy) in the operating room. The empirical intravitreal antibiotics most often used in the United States are vancomycin, 1 mg, plus ceftazidime, 2.25 mg. Each agent is diluted in 0.1 mL of sterile water or normal saline. Amikacin, 0.4 mg, may be used in place of ceftazidime for patients with significant cephalosporin allergies or for treatment of ceftazidime-resistant organisms, but in general, intravitreal aminoglycosides are avoided due to the risk (although very rare) of macular infarction.[85] Macular infarction from intravitreal aminoglycosides causes a blind eye, and there is no known treatment.[86]

Intravitreal antibiotics persist in the vitreous only 24 to 48 hours.[87] In severe cases of endophthalmitis one antibiotic injection may be insufficient to cure the infection. This is especially true in patients who did not undergo a vitrectomy as their initial procedure but only an office tap and inject. If such patients fail to improve by 24 to 48 hours, a vitrectomy with repeat antibiotics (either vancomycin or ceftazidime) is usually indicated. Vitrectomy rather than a tap is in fact the initial procedure of choice in patients presenting with fulminant infection because a vitrectomy débrides the abscess-like infected vitreous rapidly, leading to quicker clearing of infection and improved visual outcome.[16,88]

Systemic antibiotics alone are not effective for treating any type of endophthalmitis but are used for treating the underlying systemic infection in endogenous endophthalmitis cases. Whether systemic antibiotics that achieve good vitreous levels and target the most common pathogens could be beneficial as adjunctive therapy in treating exogenous bacterial endophthalmitis is unknown. Theoretically, such systemic antibiotics could effectively extend the half-life of intravitreal antibiotics. The only large randomized trial undertaken to evaluate this was the Endophthalmitis Vitrectomy Study (EVS), which evaluated patients with postcataract endophthalmitis.[16] The EVS concluded that the addition of systemic antibiotics to intravitreal antibiotics was not beneficial, but the systemic antibiotics used in the study (IV amikacin plus ceftazidime) had poor efficacy against staphylococci, the etiology of 80% of cases. In addition, amikacin penetrates the blood-eye barrier poorly.[83,89] The value of adjunctive intravitreal corticosteroids (dexamethasone, 0.4 mg) is unknown because no large randomized controlled trials (RCTs) have been conducted. A 2017 Cochrane review of the literature identified only three randomized trials, none listed in a clinical trial registry, and these had a combined total of only 95 participants.[90] The review concluded that the effectiveness of adjunctive corticosteroid therapy could not be determined based on available literature. In acute bacterial endophthalmitis of any type (postcataract, endogenous, bleb-related), removal of any synthetic IOL that is present is usually not necessary. In chronic pseudophakic endophthalmitis, exchange or removal of the IOL is necessary in the majority of cases. In mold endophthalmitis the IOL should be removed.

Chronic Postcataract Endophthalmitis

Chronic postcataract endophthalmitis due to *P. acnes* requires at least vitrectomy and intravitreal vancomycin for treatment, but 50% of cases recur with this therapy alone.[91] The addition of posterior capsulectomy to this regimen reduced the recurrence rate in one study,[91] but not in another.[92] Exchanging the IOL for a new one markedly improved the success rate. The combination of total capsulectomy, IOL exchange or removal, vitrectomy, and intravitreal antibiotics cured all infections in both studies, including refractory infections that had failed earlier therapies. Systemic antibiotic therapy is not indicated for this condition.

Fungal Endophthalmitis

Endogenous *Candida* Endophthalmitis

All patients with ocular candidiasis require systemic antifungal therapy. Patients with *Candida* chorioretinitis but no endophthalmitis (i.e., minimal or no vitritis) usually respond to systemic antifungal therapy alone. In patients with chorioretinitis in which there is a macula-threatening lesion, intravitreal antibiotics are recommended in addition, to provide immediate high intraocular antifungal levels. The intravitreal antibiotics used are amphotericin, 5 to 10 μg in 0.1 mL sterile water, or voriconazole, 100 μg in 0.1 mL sterile water. Voriconazole may be used for sensitive strains.

Treatment of endogenous *Candida* endophthalmitis (i.e., significant vitritis) includes immediate intravitreal antifungal therapy in addition to systemic antifungal therapy in all patients and a vitrectomy in nearly all cases. Vitrectomy is performed with local (retrobulbar) anesthesia rather than general anesthesia, but vitrectomy still may not be possible in very ill inpatients with candidemia. However, vitrectomy appears to be beneficial in patients with significant vitritis. A study of 12 patients with *Candida* endophthalmitis (i.e., significant vitritis) reported a good outcome in the 7 patients who underwent early vitrectomy, but blindness or scotoma in 4 of 5 patients in whom vitrectomy was delayed more than 1 week or not performed.[93]

Systemic therapy is indicated for both *Candida* chorioretinitis and endophthalmitis. Systemic fluconazole and voriconazole achieve excellent vitreous levels (70% and 40%, respectively, of plasma levels), and these agents are favored over amphotericin due to better intraocular penetration and lower systemic toxicity.[94] For endophthalmitis due to fluconazole-susceptible *Candida* strains, fluconazole is the treatment of choice and is prescribed as a loading dose of 800 mg (12 mg/kg), followed by 400 to 800 mg (6–12 mg/kg) daily. The dose is reduced for patients with renal dysfunction. Although some fluconazole-resistant *Candida* species are also voriconazole resistant, voriconazole should be used for voriconazole-susceptible strains, or in patients intolerant of fluconazole but tolerant of voriconazole. Voriconazole is given as a loading dose of 400 mg (6 mg/kg) IV twice daily for 2 doses, followed by 200 to 300 mg (4 mg/kg) IV or orally twice daily. Voriconazole has more drug-drug interactions and is more expensive than fluconazole, and serum voriconazole levels should be monitored beginning approximately 1 week after starting therapy. In cases of endophthalmitis caused by *Candida* strains that are resistant to fluconazole and voriconazole, the 2016 Infectious Diseases Society of America guidelines recommend IV liposomal amphotericin (3–5 mg/kg, IV daily), with or without flucytosine, 25 mg/kg four times daily.[95,96,97]

Echinocandins successfully treat most cases of candidemia, including candidemia due to fluconazole-resistant strains. However, they are not recommended for treating *Candida* endophthalmitis due to poor penetration into the vitreous. It is possible, but not proven, that echinocandins may be adequate to treat *Candida* chorioretinitis. A study of eight eyes in seven patients who were receiving IV micafungin at the time of vitrectomy or enucleation demonstrated very poor micafungin levels in the vitreous (average 0.5% of plasma levels), but a good level in the choroid in the one eye in which this was measured (5.8 μg/mL, or 34% of plasma level).[98] There have been case reports of failure in endophthalmitis (significant vitritis) but success in chorioretinitis.[99,100] In addition, a large randomized prospective trial of echinocandins (micafungin vs. caspofungin) for treating invasive candidiasis included 11 patients with *Candida* chorioretinitis, and 7 (64%) had successful outcomes.[101] The study does not mention whether adjunctive therapies were used (vitrectomy, intravitreal antifungal agents).

Exogenous *Candida* Endophthalmitis

Many cases of exogenous *Candida* endophthalmitis primarily involve the aqueous humor, and these may be treated with either intracameral amphotericin or voriconazole (for susceptible strains). The usual dose is 5 μg of amphotericin or 50 μg of voriconazole. Voriconazole is preferred over amphotericin for sensitive species because intracameral amphotericin can cause a transient increase in eye pain, hypopyon, or intraaqueous inflammation.[102,103] Intracameral voriconazole has a half-life of only 22 minutes in rabbits,[104] so a similarly short half-life is presumed in humans.

Topical voriconazole 1% solution applied to the cornea every 2 hours in one study produces high levels in the aqueous after 24 hours,[105] so topical voriconazole may be given at regular intervals to prolong the intracameral level of the drug after intracameral injection. Antibiotics injected into the aqueous do not usually reach the vitreous, so a separate intravitreal injection of either amphotericin (5–10 μg) or voriconazole (100 μg) should be given in most cases. Even in cases in which there is no apparent vitritis, intravitreal injection of antifungal agent should be considered (in addition to intracameral antifungal) because occult infection may already be present. In cases in which there is marked vitritis, vitrectomy should be performed in addition to intravitreal amphotericin or voriconazole. Systemic fluconazole (for susceptible strains) or voriconazole (for fluconazole-resistant strains, such as *Candida krusei* or some strains of *Candida glabrata*) is recommended in all cases of exogenous *Candida* endophthalmitis, in addition to intravitreal antifungal therapy.

In nearly all cases of postcataract *Candida* endophthalmitis, the IOL should be removed. In cases that occur after corneal transplantation, the infected cornea is often replaced with a new donor cornea at the onset of endophthalmitis.

Mold Endophthalmitis

Mold endophthalmitis should be treated with a combination of vitrectomy, intracameral and/or intravitreal antifungal therapy, removal of any foreign material such as an IOL, and systemic antifungal therapy.

In cases of exogenous endophthalmitis primarily involving the aqueous, such as occurs with progression of keratomycosis, intracameral amphotericin, 5 μg, or voriconazole, 50 μg, should be given in addition to systemic voriconazole (for susceptible fungi). Any foreign material, such as an IOL, synthetic glaucoma filtering valve, or foreign body introduced by trauma, must be removed. For cases resulting from progression of fungal keratitis, corneal transplantation is almost always required when endophthalmitis is diagnosed, to rapidly debulk the infection. An intravitreal injection of amphotericin or voriconazole is often given in exogenous cases even if there is no apparent vitritis because of concern for occult infection. Patients with exogenous mold endophthalmitis involving the vitreous should receive a vitrectomy plus intravitreal amphotericin, 5 to 10 μg, or voriconazole, 100 μg (for susceptible fungi),[106,107–108] plus systemic voriconazole (for susceptible fungi). Intravitreal injections of either amphotericin or voriconazole may be repeated at least 48 hours after the first injection if there is no improvement and may be repeated more than once if necessary.

Systemic voriconazole is recommended for all cases of exogenous mold endophthalmitis due to susceptible molds, such as *Aspergillus* and *Fusarium*.[109,110] These molds are the most common causes of exogenous and endogenous mold endophthalmitis, and systemic voriconazole achieves good intraocular levels. IV voriconazole is preferred for initial treatment to ensure adequate levels before switching to oral therapy. For cases of exogenous endophthalmitis involving the vitreous and due to voriconazole-resistant molds, adjunctive liposomal amphotericin may be given in addition to vitrectomy and intravitreal amphotericin injections (and removal of IOL, etc.). However, the potential risk of toxicity versus benefit of adjunctive systemic liposomal amphotericin therapy must be weighed for a particular case, and this evaluation must take into account the response to initial vitrectomy and intravitreal amphotericin. Systemic therapy with posaconazole has been used with success in a few case reports.[111,112] Fluconazole is not recommended due to poor activity against molds. Use of isavuconazole for treating mold endophthalmitis has not been reported.

Treatment for endogenous mold endophthalmitis due to transient fungemia (e.g., after IVDU) includes vitrectomy, intravitreal amphotericin or voriconazole, and systemic voriconazole (for susceptible molds). For endogenous cases in patients ill with fungemia, the systemic antifungal chosen should be the one optimal for the systemic infection. Such patients are often too ill for vitrectomy but can tolerate intravitreal injections of antifungal agents.

VISUAL OUTCOME

The final visual outcome after acute bacterial endophthalmitis usually cannot be determined for several months because sequelae of intraocular inflammation resolve slowly. Patients who lose all vision (no light perception) almost never regain it, however. Some predictions can be made based on presenting visual acuity and the causative organism, factors that are related. In the EVS, patients who presented with the worst vision—light perception only—were much more likely to have infection from virulent bacteria (streptococci, *S. aureus,* gram-negative bacilli) and a poor visual outcome. Factors that correlated with virulent bacteria in the EVS included presentation with swollen eyelids, afferent pupillary defect, corneal infiltrate, larger hypopyon (≥1.5 mm), or loss of a red reflex.[113] Patients did best if they presented with a mild decrease in vision or had vitreous cultures that were negative or grew coagulase-negative staphylococci. In the EVS, outcome closely correlated with the pathogen recovered.[114] Greater than 80% of eyes with coagulase-negative staphylococci had at least 20/100 vision at follow-up 9 to 12 months later, and only 4% had severe visual loss (<5/200). Results in culture-negative endophthalmitis cases were similar. In contrast, 20/100 or better vision was achieved in only 56% of gram-negative cases, 50% of *S. aureus* cases, and 30% of streptococcal cases. Similar large outcome studies are not available for other types of endophthalmitis, but in general, outcomes reflect the virulence of the predominant organisms. Some of the worst outcomes are seen in posttraumatic endophthalmitis due to *B. cereus,* in which salvage of the eye is rare.[115] The generally poor visual outcome in bleb-related endophthalmitis reflects the fact that most cases are due to streptococci and *H. influenzae.* Endogenous bacterial endophthalmitis also usually has a poor outcome, although early diagnosis and prompt treatment with vitrectomy and intravitreal antibiotics has saved useful vision even in eyes with virulent organisms.[40]

Visual outcome after chronic *P. acnes* endophthalmitis may depend on the chronicity of the infection. In a review of 36 patients diagnosed with this infection over 22 years, the visual outcome was 20/40 or better in half of the patients but worse than 20/400 in one-fifth of patients.[91]

The visual prognosis for endogenous *Candida* endophthalmitis is difficult to determine because many reviews combine cases of chorioretinitis with endophthalmitis cases.[42] Patients with chorioretinitis alone usually have excellent visual outcomes. *Candida* endophthalmitis also may have a good outcome if treated with vitrectomy, intravitreal antifungal therapy, and systemic therapy. The prognosis in mold endophthalmitis in the pre-voriconazole era was poor, with rare salvage of useful vision. However, several recent cases treated in the voriconazole era with the aggressive management described earlier have had excellent visual outcomes (20/20–20/60).[116,117]

PREVENTING ENDOPHTHALMITIS

Prophylaxis for Eye Surgery

The value of any type of prophylaxis for postoperative endophthalmitis is unknown.[118,119,120] Standard prophylaxis involves only the use of topical povidone-iodine on the conjunctiva and eyelids immediately before surgery. A multicenter European study, European Society of Cataract and Refractive Surgeons (ESCRS), conducted from 2003–06 found that use of prophylactic intracameral (into the anterior chamber) cefuroxime, 1 mg/0.1 mL, at the end of cataract surgery was associated with a significantly lower rate of endophthalmitis than non-use, 0.06% versus 0.3%.[121] As a consequence, many centers worldwide now use this prophylaxis. Adoption of intracameral cefuroxime prophylaxis has not been universal, however, because of criticism that the ESCRS control group's endophthalmitis rate was surprisingly high (0.3%, whereas typical rates are 0.1%). Although adoption of intracameral cefuroxime prophylaxis has reduced endophthalmitis rates in some centers, other sites have not seen a benefit.[122] The ESCRS study was the only RCT to evaluate intracameral antibiotic prophylaxis. Ophthalmologists have used other intracameral antibiotics for prophylaxis, such as intracameral moxifloxacin or vancomycin, without benefit of RCTs.[123] However, since 2014, a rare but potentially blinding adverse reaction to prophylactic intraocular vancomycin has been described. This reaction is labeled "hemorrhagic occlusive retinal vasculitis" and is of unknown etiology, although clearly associated with recent intraocular vancomycin injection.[124,125,126] Symptoms include a delayed onset of painless vision loss (1–21 days), mild aqueous and vitreous inflammation, retinal hemorrhages in areas of ischemia, and involvement of retinal venules.[126] Visual

outcomes have been very poor, with 67% of eyes left with 20/200 or worse vision and 20% left with no light perception.[126] Intraocular vancomycin should not be given for prophylaxis.

The value of giving postoperative topical antibiotics is also unknown, and no RCT has assessed this. However, ophthalmologists commonly prescribe postoperative topical antibiotics, partly due to the concern about potential contamination postoperatively through a clear cornea incision. In Sweden, where prophylactic intracameral cefuroxime is used but topical postoperative antibiotics are not, endophthalmitis rates are low.[118]

Prophylaxis for Intravitreal Injections

Intravitreal injections are performed as an office procedure, and gowns, gloves, and masks are rarely used. However, the high incidence of postinjection endophthalmitis caused by viridans streptococci has led to the realization that the ocular surface may be contaminated by oral flora from either the patient or the ophthalmologist during the procedure. As a consequence, use of masks or observing silence in the room during the injection is recommended.[118,120] Topical antibiotics should not be used for prophylaxis after intravitreal anti-VEGF injections because these have been associated with an increased risk of postinjection endophthalmitis.[127]

Prophylaxis for Eye Trauma

Prompt repair of penetrating eye (open globe) injuries is important in preventing posttraumatic endophthalmitis. A brief course of prophylactic antibiotics at the time of presentation with an open globe appears to be beneficial, based on the results of several series.[31,33,128,129] Two centers have achieved very low rates of posttraumatic endophthalmitis (0.9%) using a prophylactic regimen of IV vancomycin plus either ceftazidime (one center) or cefepime (the other center).[33,129] Prophylactic antibiotics are started on presentation and continued for 48 hours.

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115 Infectious Causes of Uveitis

Marlene L. Durand

SHORT VIEW SUMMARY

Definition and Categories

- *Uveitis* means inflammation of the uvea (iris, ciliary body, choroid) or retina.
- Uveitis is divided into categories by the site of greatest inflammation:
  - Anterior (iritis, iridocyclitis)
  - Intermediate (pars planitis)
  - Posterior (choroiditis, retinitis, chorioretinitis)
  - Panuveitis
- Noninfectious causes of uveitis (idiopathic, autoimmune) are more common than infectious causes, but the frequency of each varies depending on category.
- Approximately 10% of anterior uveitis cases have an infectious etiology.
- Approximately 50% of posterior uveitis cases have an infectious etiology.

Epidemiology and Etiology

- The most likely infectious etiologies vary by uveitis category and by location in the world (see Table 115.1).
- Infectious causes of anterior uveitis include herpes simplex virus (HSV) (90% of infectious etiologies), varicella-zoster virus (VZV), syphilis, tuberculosis (TB), and Lyme disease.
- Infectious causes of intermediate uveitis are rare and include Lyme disease.
- Infectious causes of posterior uveitis include ocular toxoplasmosis, acute retinal necrosis (HSV, VZV, sometimes cytomegalovirus [CMV]), CMV retinitis (severely immunocompromised patients), ocular *Toxocara,* syphilis, cat-scratch disease, and *Candida* endophthalmitis. West Nile virus may cause uveitis, most commonly a multifocal chorioretinitis
- Infectious causes of panuveitis include syphilis, TB, and *Candida* endophthalmitis.
- Some bacterial etiologies of uveitis are seen primarily in tropical regions or developing countries; these include leptospirosis (panuveitis without retinal or choroidal lesions), leprosy (anterior uveitis), and *Brucella* (chronic relapsing uveitis). Viral infections caused by Chikungunya virus, Ebola virus, and Zika virus may also produce various types of uveitis.

Diagnosis

- Diagnosis varies by etiology; see text. Ocular syphilis is presumed in cases of uveitis with positive specific treponemal serology. Polymerase chain reaction of aqueous or vitreous for HSV, VZV, and CMV may be helpful in some chronic anterior uveitis cases (aqueous) and in some cases of acute retinal necrosis (vitreous higher yield than aqueous, but vitreous sampling carries more risk).

Therapy

- Therapy varies by etiology; see text. Acute retinal necrosis is a medical emergency and requires antiviral treatment directed against HSV and VZV; consider treatment that is also effective against CMV in immunocompromised patients. Ocular toxoplasmosis is discussed in Chapter 278. Ocular TB and ocular syphilis should be treated the same way as TB meningitis and neurosyphilis, respectively.

Uveitis means inflammation of the uvea. The uvea is the pigmented, vascular middle layer of the eye embryologically, sandwiched between the cornea-sclera outer protective layer and the retina. The word *uvea* comes from the Latin word *uva,* meaning *grape,* a translation by Roman anatomists (e.g., Galen) of the Greek term, used because of the grapelike appearance of this highly vascular layer when the white sclera was stripped away. The uvea is composed of the iris, ciliary body, and choroid (see Chapter 111). The *iris* regulates the amount of light that reaches the retina, the *ciliary body* produces aqueous humor and supports the lens, and the *choroid* helps to nourish the retina.

Retinitis is included as a type of uveitis even though the retina is not part of the uvea because the retina is often involved when there is underlying choroidal inflammation. Uveitis is classified by the ocular structures involved. Several anatomic classification schemes exist, but all divide uveitis into anterior, intermediate, posterior, and panuveitis categories (Table 115.1). The site of greatest inflammation determines the category. The International Uveitis Study Group classification is commonly used. In anterior uveitis, inflammation involves the iris (iritis), anterior ciliary body (cyclitis), or both (iridocyclitis). Anterior uveitis is characterized by white blood cells (WBCs) in the aqueous humor. There are often keratic precipitates (cells on the corneal endothelial surface) and iris lesions. Intermediate uveitis refers to inflammation involving the anterior vitreous, ciliary body, and adjacent portion of the retina (called *peripheral* retina). Posterior uveitis refers to inflammation involving the choroid (choroiditis), the retina (retinitis), both the choroid and the retina (chorioretinitis), or the retinal vessels (retinal vasculitis). There may be inflammation of the vitreous and/or optic nerve. Panuveitis involves all three parts of the uvea. Uveitis may also extend to involve the cornea (keratouveitis) or sclera (sclerouveitis).

Other terms commonly used in uveitis appear in Fig. 111.1 in Chapter 111. The eye is divided into anterior and posterior segments by the lens. The iris divides the anterior segment further into anterior and posterior chambers. Aqueous humor fills the anterior segment and is produced and resorbed constantly, with a turnover time of 100 minutes. The posterior segment, a term not to be confused with posterior chamber, is filled with the gel-like vitreous. The vitreous is produced in utero and never regenerated, although it may be surgically removed (vitrectomy) and replaced with clear fluids such as saline.

In addition to anatomic location, uveitis is classified as granulomatous or nongranulomatous. *Granulomatous* does not mean there are granulomas on pathology, but rather describes a type of inflammation in which the WBCs are condensed into clumps rather than uniformly dispersed. In granulomatous anterior uveitis, *granulomatous* or *mutton fat* keratic precipitates form on the endothelial surface of the cornea. These are greasy in appearance and more yellow than nongranulomatous *(granular)* keratic precipitates (Fig. 115.1). There may also be clusters of WBCs in the iris, called *Busacca nodules* if in the iris stroma and *Koeppe nodules* if at the pupillary margin. Topical corticosteroid treatment may convert a granulomatous anterior uveitis into a nongranulomatous anterior uveitis. In granulomatous uveitis that involves the posterior segment of the eye, there may be WBCs in large clusters *(snowballs)* in the vitreous, in exudates adjacent to retinal vessels *(candle wax drippings)*, or as granulomas within the choroid (e.g., multifocal choroiditis). Granulomatous uveitis is typical of infections such as tuberculosis (TB), syphilis, and toxoplasmosis, although all may have a nongranulomatous presentation. Two types of autoimmune uveitis, sarcoidosis and Vogt-Koyanagi-Harada syndrome, usually produce a granulomatous uveitis. Nongranulomatous inflammation is more characteristic of autoimmune

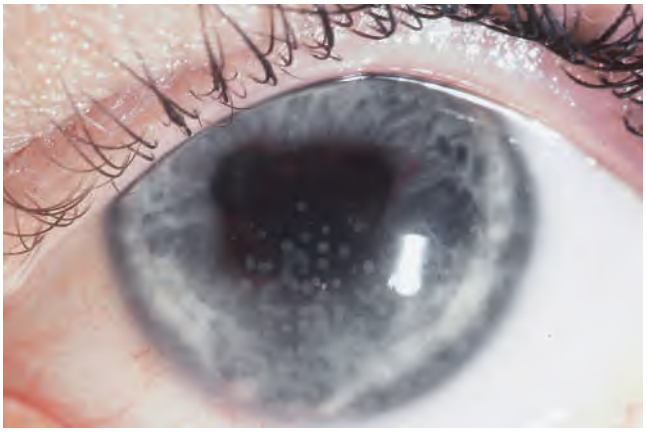

FIG. 115.1 Granulomatous keratic precipitates. Granulomatous keratic precipitates, also called *mutton fat* keratic precipitates. The white precipitates represent white blood cells that have condensed on the endothelial surface of the cornea in anterior uveitis. They do not represent granulomas. Granular keratic precipitates are similar, but the condensations are much smaller, so the white "dots" appear finer. *(Courtesy Audrey C. Melanson.)*

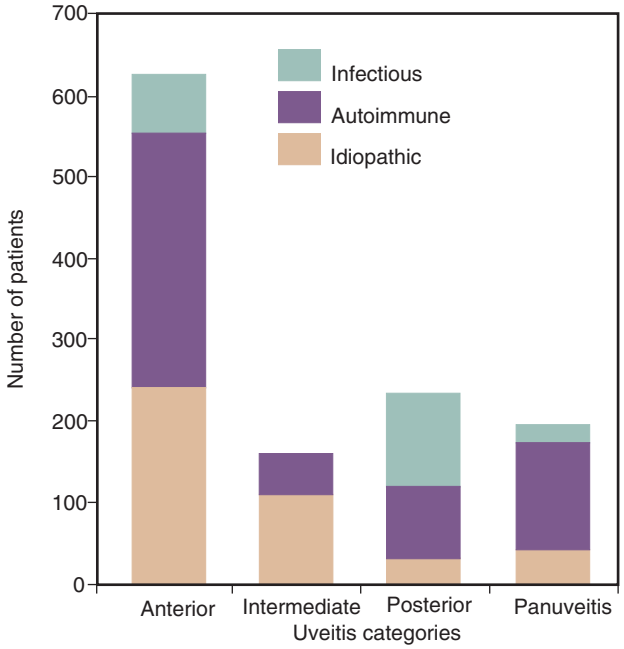

FIG. 115.2 Etiologies of uveitis. Bar graph of the causes of uveitis by anatomic category (anterior, intermediate, posterior, panuveitis), one bar for each category. Each bar is divided into three segments, a different color for each etiology: infectious, autoimmune, and idiopathic. *(Height of each bar and each segment based on data by Rodriguez A, Calonge M, Pedoza-Seres M, et al. Referral patterns of uveitis in a tertiary eye care center.* Arch Ophthalmol. *1996;114:593–599.)*

TABLE 115.1 Classification of Uveitis and Major Infectious Etiologies in Each Category

CATEGORY	OCULAR FINDINGS	MAJOR INFECTIOUS ETIOLOGIES (%)[A]
Anterior (iritis, cyclitis, iridocyclitis)	WBCs in aqueous, keratic precipitates, iris nodules, synechiae	Herpes simplex (10%); syphilis (<1%); TB (<1%); Lyme disease (<1%); leprosy (<1%)
Intermediate	WBCs or *snowballs* in vitreous, pars plana *snow bank*	Lyme disease (<1%)
Posterior (choroiditis, chorioretinitis, retinitis)	Lesions in choroid, retina, or both; vitritis in some	*Toxoplasma* (25%); CMV (12%)[b]; ARN (6%); *Toxocara* (3%); syphilis (2%); *Candida* (<1%)
Panuveitis	WBCs in aqueous and vitreous	Syphilis (6%); TB (2%); *Candida* (2%)

[a]Percentage of uveitis cases in each category (not of total uveitis cases), based on 1237 cases of uveitis seen at Massachusetts Eye & Ear Infirmary, Boston, 1982–92. (Rodriguez A, Calonge M, Pedoza-Seres M, et al. Referral patterns of uveitis in a tertiary eye care center. *Arch Ophthalmol.* 1996;114:593–599.)
[b]Series was before use of highly active antiretroviral therapy, and rate for CMV retinitis would be lower now.
ARN, Acute retinal necrosis; *CMV,* cytomegalovirus; *TB,* tuberculosis; *WBCs,* white blood cells.

uveitis such as Behçet disease, reactive arthritis, and ankylosing spondylitis.

EPIDEMIOLOGY

Uveitis has a prevalence of 70 to 115 cases/100,000 population in the United States and may account for up to 10% of blindness worldwide.[1,2] Uveitis can occur at any age but is less common in children than in adults. Surveys from around the world report a mean age at presentation of 35 to 45 years old.[3] Uveitis is more common in women than men in most studies. Anterior uveitis is the most common type of uveitis, accounting for up to 90% of uveitis cases in community-based ophthalmology practices.[4–6] Major referral eye centers report a relatively high incidence of posterior and panuveitis cases, likely due to the vision-threatening nature of these conditions. A large study from a referral center in India reported that posterior uveitis (11%) and panuveitis (22%) accounted for one-third of cases, whereas intermediate (10%) and anterior (57%) uveitis accounted for the remaining cases.[3]

Uveitis may be caused by autoimmune conditions, infections, or, rarely, trauma, but up to 50% of cases are idiopathic. Some cases of intraocular inflammation masquerade as uveitis (masquerade syndromes) but have other causes such as malignancy (e.g., ocular–central nervous system [CNS] lymphoma).

Infections cause approximately 20% to 50% of uveitis cases, with the higher frequency seen in tropical countries. The most common infectious etiology varies by country and region. In Iran, infections caused 20% of uveitis cases with herpetic infections and TB as the most common infectious etiologies.[7] In a South African study, infections accounted for 47% of uveitis cases, with syphilis (16%) being the most common infectious etiology,[8] whereas a study from Vietnam reported an infectious etiology in 27% of uveitis cases, with the most common being TB (9%).[9]

The likelihood of an infectious etiology is greater in some categories of uveitis, such as posterior uveitis, than others. This is illustrated in Fig. 115.2, and the frequency of infections is listed by category in Table 115.1. Understanding the types of infectious etiologies by category is helpful in considering possible etiologies for a patient with uveitis. In anterior uveitis cases in the United States, most cases are idiopathic (40%) or associated with a rheumatologic condition (45%) such as seronegative arthropathies, human leukocyte antigen (HLA)-B27–associated disease, reactive arthritis, and juvenile rheumatoid arthritis. The most common infectious cause is herpes simplex, which accounts for almost 10% of anterior uveitis cases, whereas syphilis, TB, and Lyme disease each cause less than 1%. Intermediate uveitis most often has an unknown etiology (69%) in the United States or is due to sarcoidosis (22%) or multiple sclerosis (8%); infections are extremely rare.[5] However, in India, intermediate uveitis has an infectious etiology in 11% of cases including leptospirosis (7%) and TB (4%).[3] Posterior uveitis has an infectious etiology in more than 40% of cases, with ocular toxoplasmosis the most common cause, accounting for 20% to 40% of posterior uveitis cases. Other infectious causes include cytomegalovirus (CMV) retinitis, acute retinal necrosis (ARN), *Toxocara,* syphilis, and *Candida* in the United States. Major noninfectious diagnoses in a US study were lupus erythematosus, sarcoidosis, and birdshot retinochoroidopathy, an eye disease of unknown etiology (8% each).[5] In panuveitis, infections cause 10% of cases and include syphilis, TB, and *Candida.*[5] The remaining

90% of cases are caused by inflammatory conditions such as sarcoidosis, Behçet disease, systemic lupus erythematosus, multifocal choroiditis and panuveitis, and Vogt-Koyanagi-Harada syndrome or are idiopathic.

CLINICAL MANIFESTATIONS

Because infectious uveitis usually represents a chronic process, patients often present with no systemic complaints. Patients with anterior uveitis typically present with eye pain and decreased vision. The eye is often injected, especially near the limbus *(ciliary flush)*, and slit-lamp examination shows cells in the anterior chamber. There may be keratic precipitates, iris nodules, or synechiae (adhesions) between the iris and either the cornea or the lens. The vitreous has few, if any, cells, and the retina is normal. Patients with intermediate uveitis present with floaters or blurred vision but typically no pain or photophobia. The aqueous is quiet, but vitreous cells are characteristic and are often clumped into so-called snowballs. There may be a white exudate or *snow bank* over the pars plana. In posterior uveitis, patients often have painless loss of vision as their primary symptom. There are usually few cells in the anterior chamber, but the funduscopic examination shows lesions in the retina or choroid or both. There may be retinal vasculitis or periphlebitis (venous sheathing). There may be many cells in the vitreous, typical of toxoplasmosis, or no vitritis, typical of CMV retinitis. Panuveitis is characterized by inflammation in both anterior and posterior segments of the eye.

Different pathogens produce different clinical manifestations when they infect the eye. The following is an alphabetical list of various infectious etiologies of uveitis and the most common clinical manifestations of each. Some of these infectious causes of uveitis are common worldwide (e.g., anterior uveitis due to herpes simplex, or posterior uveitis due to ocular toxoplasmosis), while others are rare (e.g., brucellosis, Whipple disease). Still others are rare except in outbreak situations (e.g., Ebola virus).

Acute Retinal Necrosis

Acute retinal necrosis (ARN) is a rapidly progressive necrotizing retinitis that mainly affects immunocompetent patients. The etiology of nearly all cases is herpes simplex virus (HSV) or varicella-zoster virus (VSV).[10] In immunocompromised patients, CMV may also be the etiology. The American Uveitis Society has established the following four features as diagnostic criteria for ARN: (1) focal well-demarcated areas of retinal necrosis located in the peripheral retina, (2) rapid circumferential progression of necrosis, (3) occlusive vasculopathy, and (4) prominent inflammation (WBCs) in the vitreous and aqueous.[10] A study of 18 patients with ARN (negative for human immunodeficiency virus [HIV]) who underwent vitreous biopsy found polymerase chain reaction (PCR) evidence of VZV in 12 specimens and HSV in 4 specimens; 2 specimens were negative by PCR.[11] CMV is a rare cause of ARN but must be considered in immunocompromised patients. Epstein-Barr virus (EBV) has been found by vitreous PCR in some cases of ARN, but only in cases in which vitreous PCR was also positive for VZV.[11] Some patients with ARN due to HSV have a history of congenital herpes or herpes encephalitis months to years earlier, but these cases are uncommon.[12,13] ARN typically begins with a unilateral anterior uveitis. Patients may have mild eye pain or photophobia followed by decreased vision in the affected eye. Funduscopic examination with an indirect ophthalmoscope shows one or more foci of retinal necrosis in the peripheral retina, an area not usually seen with a direct ophthalmoscope (Fig. 115.3). The areas of retinitis have sharply demarcated borders and typically spread circumferentially and posteriorly. Vascular sheathing develops along with a dense vitritis. Necrosis of areas of the retina leads to retinal detachment in many patients. Retinal detachment occurs weeks to months after onset of ARN. One study found that more than 50% of patients developed a retinal detachment, and this occurred 3 weeks to 5 months after onset of ARN.[11] Treatment with laser to encircle areas of retinal necrosis may help prevent retinal detachment. Treatment with intravenous acyclovir halts progression of the retinitis in ARN in most cases. ARN may involve the other eye several months after the first eye even despite therapy. In an early study, ARN developed in the other eye in 70% of patients who had not received antiviral treatment and in 13% of treated patients.[14] In cases that progress despite intravenous acyclovir, intravitreal foscarnet and other systemic antiviral agents may be essential to halt the rapid progression of this blinding infection (see "Therapy").

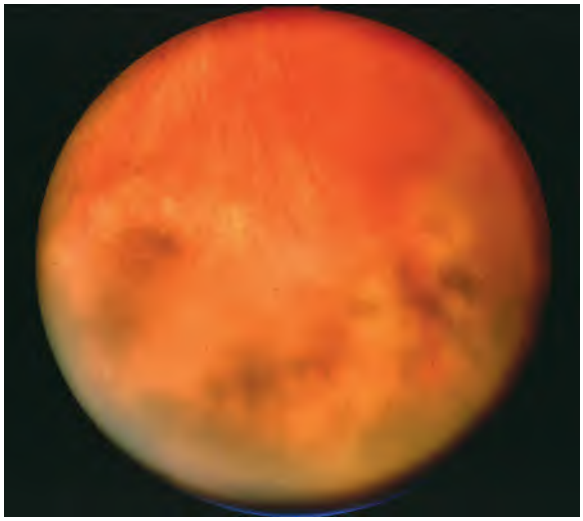

FIG. 115.3 Acute retinal necrosis. Funduscopic photograph of acute retinal necrosis showing loss of retinal features in the peripheral retina due to retinal necrosis.

Brucellosis

Brucellosis is one of the most widespread zoonoses worldwide, with endemic regions in the Middle East, Africa, Central Asia, India, China, and Central and South America. Cases may be seen in nonendemic countries in travelers or immigrants from endemic regions. Uveitis may develop as part of the illness. A prospective study from Turkey of 147 patients with brucellosis found uveitis in 5% (anterior in 6 patients and posterior in 1 patient).[15] The authors noted that osteoarticular complications of brucellosis such as spondylitis were more common in patients with ocular involvement. Ocular involvement may occur during acute or chronic brucellosis. A report from Iran described a case of bilateral acute optic disk swelling with retinal hyperemia occurring 1 week after the febrile illness.[16] Chronic relapsing uveitis may be a sign in chronic, untreated brucellosis. In a 2008 study of 1551 patients with brucellosis seen in Peru over a 26-year period, 0.7% of patients with acute brucellosis and 8% of patients with chronic brucellosis had ocular findings.[17] Uveitis accounted for more than 80% of cases, with posterior uveitis accounting for half of the cases. The diagnosis of brucellosis may be missed for years. Tabbara and Al-Kassimi[18] described a Saudi Arabian patient with a 9-year history of relapsing uveitis with episodes responding to corticosteroids. The patient also had a history of recurrent fevers, but brucellosis was not diagnosed until she developed a paravertebral abscess due to *Brucella melitensis*. The uveitis responded to antibiotic therapy.

Cat-Scratch Disease

Bartonella henselae causes Parinaud oculoglandular syndrome in 2% to 5% of patients with cat-scratch disease (CSD). This syndrome consists of a necrotic granuloma with ulceration of the conjunctival epithelium and regional lymphadenopathy (preauricular, submandibular, cervical). The other major ocular manifestations of CSD are neuroretinitis and optic neuritis, although other posterior segment manifestations (e.g., vitritis, focal retinitis, choroiditis, intraretinal white spots, retinal vasculitis) have been described.[19] Most cases of presumed ocular CSD rely on positive serologic testing for *B. henselae* for diagnosis, so it is possible that some of these cases have another etiology but a positive CSD serology from prior and unrelated cat exposure. Rare cases have had positive PCR testing of intraocular fluids. *Bartonella grahamii* has been identified by PCR amplification and sequence analysis in the intraocular fluid of an HIV-seronegative patient with bilateral neuroretinitis and behavioral changes; *Bartonella elizabethae* has been

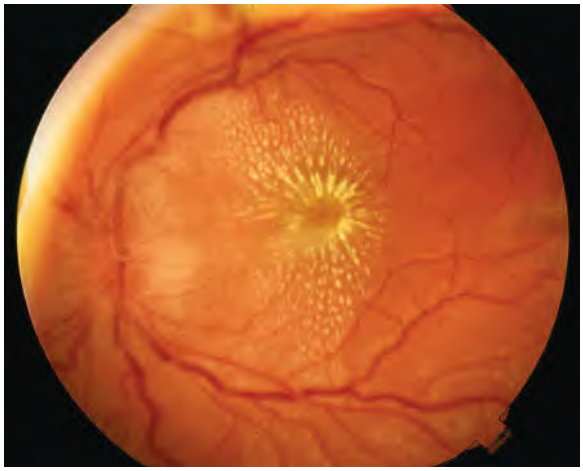

FIG. 115.4 Cat-scratch disease neuroretinitis. Funduscopic photograph of cat-scratch disease neuroretinitis, showing macular star in a 9-year-old patient who developed unilateral visual loss after acquiring a kitten. *(Courtesy Dr. Simmons Lessell.)*

implicated as the pathogen in another patient with neuroretinitis by serologic antibody studies exclusively.[20,21]

Neuroretinitis is a clinical diagnosis with characteristic eye findings of optic disk edema and a macular star, a striking sunburst pattern around the macula (Fig. 115.4). Patients present with a fairly sudden loss of vision. The macular star resolves in 2 to 3 months, and vision usually spontaneously recovers in almost all patients. Approximately two-thirds of patients with neuroretinitis are seropositive for *B. henselae*.[22] Optic neuropathy is another common manifestation of ocular CSD. In 53 patients ranging in age from 8 to 65 years with CSD-related optic neuropathy, two-thirds had flu-like symptoms at the time of presentation, including fever and headache in approximately one-fourth.[19] Bilateral involvement was present in 17%, and half also had neuroretinitis. Significant visual complications occurred in 9%, primarily due to retinal vascular occlusion. Antibiotics were given in 74%, and there was no correlation with visual outcome. Antibiotics such as doxycycline, quinolones, or macrolides, with or without rifampin, have been given to treat ocular CSD, but the benefit is uncertain.[23] The benefit of corticosteroids is also unclear. In a retrospective study of patients treated over a 20-year period in Israel, 12 of 24 eyes (50%) treated with antibiotics alone had significant visual acuity improvement versus 14 of 16 eyes (88%) treated with a combination of antibiotics plus corticosteroids, but the association with improved visual acuity and combination therapy remained significant only if doxycycline-based regimens were included.[23] The study could not answer whether antibiotics alone or corticosteroids alone were beneficial, when compared with no treatment as numbers were too small, but 100% of eyes ($n = 3$) treated with corticosteroids alone and 60% of eyes ($n = 5$) with no treatment also had significant improvement in visual acuity.

Chikungunya Virus

Chikungunya virus is transmitted by mosquitoes and causes an acute febrile illness after an incubation period of 3 to 7 days (can range from 2 to 12 days). Chikungunya virus has been reported from more than 60 countries worldwide. Major outbreaks have occurred in India; countries in the Indian and Pacific Oceans; other parts of Asia; Africa; and, since 2013, the Caribbean and South America. Cases in the United States are primarily seen in travelers who have recently returned from an endemic area; 156 cases were reported to the US Centers for Disease Control and Prevention in 2017, all in returned travelers.[24] The illness is characterized by the acute onset of high fever and severe joint pains; joint symptoms are usually bilateral and symmetrical. Uveitis typically occurs several weeks after the acute illness, although onset may be during the illness or months later. The most common eye findings are anterior uveitis (iridocyclitis), retinitis, and optic neuritis.[25,26] The retinitis or retinochoroiditis is characterized by areas of whitening in the posterior pole with surrounding retinal and macular edema; there may be an associated occlusive vasculitis.[27] Most patients recover good visual acuity.

Cytomegalovirus Anterior Uveitis

CMV has been implicated in some cases of chronic or recurrent anterior uveitis.[28] Similar to HSV and VZV, these cases have been unilateral and chronic, and some have had sectoral iris atrophy. The patients are immunocompetent and have no CMV retinitis or other signs of CMV disease. Similar to HSV and VZV, serology shows evidence of past rather than acute infection. CMV cases typically have diffuse keratic precipitates and marked intraocular pressure elevation at the time of the uveitis flares.[28] Diagnosis has been made by PCR of the aqueous. In some cases, there is response to oral valganciclovir hydrochloride. However, optimal duration of treatment is unknown. In some cases, recurrence of anterior uveitis has occurred while on therapy as well as soon after stopping the medication.[28,29] It is unclear whether local CMV reactivation is the primary cause of the uveitis or whether it reflects a secondary reactivation in response to another cause of the inflammation.[29]

Cytomegalovirus Retinitis

Although CMV may cause acute retinal necrosis in an immunocompromised host, it more typically causes a characteristic CMV retinitis. CMV retinitis affected more than 30% of patients with acquired immunodeficiency syndrome (AIDS) before highly active antiretroviral therapy (HAART), but now it is rare in countries where HAART is widely available. However, CMV was still the most common cause of ocular lesions in HIV-positive patients seen at a tertiary eye center in India from 1993 to 2010.[30] CMV retinitis is seen primarily in HIV-positive patients who are HAART-naïve or who have failed HAART; most have $CD4^+$ T-cell counts less than 50 cells/mm^3 (average 15 cells/mm^3 in one study).[31] CMV retinitis may also occur in other severely immunocompromised patients, such as organ transplant recipients. Patients with CMV retinitis usually present with painless loss of vision. Eye findings typically include white retinal infiltrates; retinal vasculitis, which may have a frosted branch angiitis pattern; and multiple retinal hemorrhages. An important clinical feature is the absence of significant vitreous inflammation. As a consequence, the view of the retina is usually clear. This is in contrast to ocular toxoplasmosis, in which vitritis is common. In one study, patients with HIV who developed CMV retinitis while on HAART had less severe disease, but more often bilateral eye involvement, than patients who were HAART-naïve.[30]

Dengue

Dengue is a flavivirus infection transmitted by mosquito bites, primarily *Aedes aegypti.* The four serotypes of dengue are widely distributed in tropical areas worldwide. Although conjunctival hemorrhage has long been recognized in dengue fever, uveitis is now increasingly being recognized and was reported in 137 of 1719 patients (7.9%) in one tertiary referral hospital.[32] Decreased vision is the most common symptom. Anterior, intermediate, and posterior uveitis may occur, with symptoms sometimes beginning months after the initial illness.[33] Macular edema or hemorrhage is the most common retinal manifestation. Involvement is bilateral in more than 70% of cases.[25] Optic neuritis also may occur. Iritis manifests as eye pain, redness, and photophobia. Prognosis for vision is good with anterior uveitis but less so in posterior segment disease.

Ebola Virus

Ebola virus disease (EVD) was first described in 1976 in central Africa, but the largest outbreak in history occurred in West Africa in 2014–16. The first case occurred December 2013, and the epidemic peaked in the fall of 2014. Greater than 28,600 cases and 11,300 deaths were reported—99.9% from Guinea, Sierra Leone, and Liberia[34]—and many of the 17,000 survivors experienced late sequelae during convalescence including uveitis. Onset of uveitis in EBV may occur weeks after recovery from the acute illness, and virus may persist in intraocular fluids for months. In 2015 a case of panuveitis developing 14 weeks after EVD onset (8 weeks after discharge from the hospital) was described, and aqueous fluid samples tested positive for Ebola virus by culture and reverse-transcription PCR.[35] The patient recovered vision after treatment

with corticosteroids and the oral antiviral favipiravir, but other EVD survivors lost vision from the uveitis. The incidence of uveitis and other ocular findings following EVD has been reported to range from 13% to 34%. A study of 96 EVD survivors in Liberia found that 22% developed EVD-associated uveitis, and 3% developed optic neuritis; 39% of eyes with uveitis had less than 20/400 vision.[36] Posterior uveitis was the most common type in this study (62% of uveitis cases). A prospective study of 341 EVD survivors in Guinea found that 14% developed uveitis, 2% developed episcleritis, and 1% developed interstitial keratitis; uveitis was most often unilateral (78%) and anterior (48%).[37] Relapses of uveitis in this study occurred up to 13 months after clearance of Ebola virus in the blood. The length of time that Ebola virus can persist in intraocular fluids has infection control implications for patients who require eye surgery. However, a study of 50 EBV survivors in Sierra Leone who required cataract surgery had no Ebola virus detected by reverse-transcription PCR in aqueous, vitreous, or conjunctival samples at a median of 19 months following EVD diagnosis.[38]

Herpetic Anterior Uveitis

Anterior uveitis due to HSV or VZV is often presumed in a patient who presents with anterior uveitis and has a history of an earlier episode of herpetic keratitis. Of the 10% of anterior uveitis cases that are due to infection, most are caused by HSV, primarily HSV type 1. The anterior uveitis represents reactivation of latent HSV infection, rather than new HSV infection, in nearly all cases. The patient is otherwise well at the time of anterior uveitis, without systemic illness, active cold sores, or other evidence of reactivation HSV infection aside from the uveitis. Most patients with HSV-related anterior uveitis have either a history of HSV keratitis or active corneal infection at the time of uveitis. HSV keratitis is common, and approximately 40% of patients with ocular herpetic disease have recurrent episodes of anterior uveitis.[39] Iritis in an eye with previous herpetic keratitis should be considered herpetic until proven otherwise.[40] Herpetic anterior uveitis is nearly always unilateral. Patients experience eye pain, redness, and photophobia. The cornea may appear cloudy, and slit-lamp examination may reveal interstitial keratitis typical of active recurrent HSV keratitis or corneal scars from prior episodes. Anterior chamber inflammation may be mild to severe, and there may be a hypopyon or keratic precipitates or both; keratic precipitates may be small, large, or stellate. Anterior uveitis due to HSV may occur in a patient with no history or findings suggesting herpetic keratitis, but this is thought to be uncommon.[41] In the absence of clinical evidence or history of HSV keratitis, some clues that may suggest herpetic anterior uveitis include unilateral disease, decreased corneal sensation, posterior synechiae, acute increase in intraocular pressure (from inflammation of the trabecular meshwork), and iris atrophy (patchy, sectoral, or diffuse).[42] VZV reactivation may cause a similar anterior uveitis. Sectoral iris atrophy is particularly suggestive of HSV or VZV as the etiology.[43] PCR studies of the aqueous in patients with no history of keratitis but recurrent episodes of anterior uveitis with sectoral iris atrophy found HSV in 83% and VZV in 13% of patients.[44]

Leprosy

More than half of patients affected by leprosy in a study from Nepal had ocular complications.[45] This was also the case in a study from India of 150 patients with leprosy, in which visual impairment was seen in 12.6% and blindness due to leprosy was seen in 3.3%.[46] Common eye findings included corneal scarring from corneal hypoesthesia and trichiasis and anterior uveitis (iridocyclitis). Most cases of ocular disease in this study and others have occurred in patients with multibacillary (lepromatous) disease of several years' duration. The uveitis in leprosy and its complications (glaucoma, cataract) are the primary cause of blindness from this disease. Uveitis is nearly always an iridocyclitis that is bilateral, chronic, and relapsing. In contrast to ocular TB, choroidal involvement is rarely seen.[47,48]

Leptospirosis

Leptospirosis is a common cause of uveitis in tropical countries and generally occurs during the immune phase of this biphasic illness. Uveitis may occur 2 days to 4 years after the initial systemic illness but usually occurs 3 to 6 months later.[49] An outbreak of uveitis involving 73 patients in southern India occurred in 1994, several months after heavy rains and flooding.[50] Uveitis was bilateral in half of the patients, and 96% had panuveitis. Nearly all patients had had a febrile illness consistent with leptospirosis 1 to 10 months earlier. Leptospiral DNA was detected by PCR in aqueous samples of 80% of patients.[51] Eye findings are typically either a nongranulomatous hypopyon uveitis or a panuveitis with marked vitritis and retinal vasculitis.[49] The retinal vasculitis affects primarily retinal veins. There may be optic disk papillitis and neuroretinitis with a macular star. Retinal and choroidal lesions are absent in leptospiral panuveitis, which helps to distinguish it from sarcoidosis, toxoplasmosis, and ARN. An analysis of 107 leptospiral uveitis cases from southern India found that several different *Leptospira interrogans* serovars were involved, but the most common was serovar Australis.[52] Some patients had infection with more than one serovar. Visual outcome did not seem to be influenced by the number or type of infecting serovars.

Lyme Disease

Uveitis rarely occurs in Lyme disease, but when it does the findings are protean. As with syphilis, ocular Lyme disease has been associated with anterior uveitis, intermediate uveitis, optic neuritis, neuroretinitis, retinal vasculitis, choroiditis, and panuveitis.[53] Uveitis is usually seen in the late stage of Lyme disease.[54] It may accompany Lyme arthritis. In a European prospective study of 84 patients with Lyme arthritis, 4% had ocular inflammation (keratitis, anterior uveitis, intermediate uveitis).[55] Intermediate uveitis, which rarely has an infectious etiology, may be the most common type of uveitis due to Lyme disease in Europe.[56] Establishing a causal relationship with Lyme disease in uveitis is complicated by the limitations of Lyme serology testing. In a retrospective study of 440 patients with optic neuritis in a hyperendemic area on Long Island, New York, Lyme disease was causal in only 1 of 28 patients with positive enzyme-linked immunosorbent assay (ELISA) tests for Lyme disease.[57] Of the remaining patients, 24 patients had a negative Lyme disease test by Western blot, and 3 had syphilis.

Presumed Ocular Histoplasmosis Syndrome

Presumed ocular histoplasmosis syndrome (POHS) is a syndrome characterized by multiple scars in the choroid *(histo spots)*, neovascularization, peripapillary atrophy, and clear vitreous and aqueous. POHS affects young and middle-aged adults and is a major cause of choroidal neovascularization in patients younger than 50 years of age. POHS causes permanent loss of vision in at least 2000 people in the United States annually and is associated with the HLA-DR15 (a subtype of HLA-DR2) and HLA-DQ6 haplotypes.[58] The etiology is unknown. Rare cases of fungal endophthalmitis have been seen in patients with disseminated histoplasmosis. A case report described acute bilateral chorioretinitis in a 16-year-old immunocompetent boy in Tennessee who developed acute disseminated histoplasmosis. Chorioretinitis did not respond to antifungal therapy alone but resolved after the eventual addition of corticosteroids. By 3 months after presentation, all chorioretinal lesions had resolved and no histo spots developed.[59] However, the association of *Histoplasma capsulatum* with POHS is presumptive and based primarily on epidemiologic grounds. In the United States, POHS is most prevalent in the Midwest, the region endemic for histoplasmosis. A study published in 1972 found that 4.4% of people living in an endemic area who tested positive by a histoplasmin skin test had ocular histo spots.[60] Other support for *H. capsulatum* as the etiology is lacking, and POHS has been found in areas where *H. capsulatum* is absent such as the Netherlands.[61]

Progressive Outer Retinal Necrosis

Progressive outer retinal necrosis (PORN) is a very rapidly progressive viral retinitis that involves the deeper ("outer") layers of the retina and occurs mainly in HIV-infected patients with low $CD4^+$ T-cell counts. It is rare in the United States and other countries in which HAART is widely available. Patients with HIV and PORN typically have $CD4^+$ counts less than 100 cells/mm^3 (average 20 cells/mm^3), but rare cases have been described in HIV-positive patients with $CD4^+$ T-cell counts

greater than 100 cells/mm^3.[62] A few cases of PORN have been described in other immunosuppressed patients such as organ transplant recipients.[63] Nearly all cases of PORN are due to VZV, although CMV and HSV have been described. Patients present with vision loss that may be unilateral or bilateral, and examination shows multiple peripheral lesions in the deep (outer) layers of the retina initially. These lesions rapidly coalesce to involve the full thickness of the retina. PORN resembles ARN but is distinguished from it clinically by the following three features: (1) involvement of the outer retina, (2) absence of any significant inflammation in the vitreous or aqueous humor, and (3) absence of involvement of the retinal vasculature. Optic neuropathy may precede PORN in rare cases.[64] The retinitis in PORN usually progresses rapidly despite systemic antiviral therapy, often resulting in blindness within days of presentation. A few successes have been achieved by a combination of systemic and intravitreal therapy (see "Therapy").

Syphilis

The incidence of ocular syphilis appears to be increasing, coincident with the rising incidence of syphilis.[65–67] Ocular syphilis may be the presenting feature of syphilis, especially in older adults.[68] Syphilis may involve the cornea as an interstitial keratitis or the sclera as a nodular scleritis.[69] Uveitis, however, is the most common manifestation of ocular syphilis and is often granulomatous. Syphilis may produce anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis. Syphilitic anterior uveitis is granulomatous in two-thirds of patients[70] and bilateral in half of patients. Interstitial keratitis, iris nodules, dilated iris vessels, and iris atrophy may be seen. The most common form of posterior uveitis is multifocal chorioretinitis, but other manifestations include focal chorioretinitis, pseudoretinitis pigmentosa, retinal necrosis, neuroretinitis, and optic neuritis. A pale optic nerve head from prior syphilitic optic neuritis may mimic glaucomatous optic atrophy. Chorioretinitis was the type of uveitis seen in 15 of 20 patients with syphilitic posterior uveitis in one review.[71] A specific type of focal chorioretinitis, acute posterior placoid chorioretinitis, has been described in syphilis for more than 20 years and is characterized by large, often solitary yellow lesions that are typically in the macula.[72] Retinal vasculitis may occur in ocular syphilis, and branch retinal vein occlusions have been described.[73]

Uveitis may occur in either congenital or acquired syphilis. Typical findings in congenital disease include interstitial keratitis and so-called salt-and-pepper fundi. Interstitial keratitis does not usually occur until the patient is a teenager or young adult. It may be accompanied by an anterior uveitis. The patient may have no other stigmata of congenital syphilis. Glaucoma may result from the inflammation. In acquired syphilis, onset of uveitis may occur in secondary or tertiary syphilis. The most common ocular finding in secondary syphilis is iritis, which accounts for more than 70% of eye findings.[73] Symptoms are often acute in onset. In contrast, when ocular syphilis develops in tertiary disease, patients often have slowly progressive decrease in vision as their only symptom. The eye findings are protean and include all of the previously listed findings. In contrast to patients with secondary disease, patients with tertiary disease are often middle-aged or older. They often have no knowledge of prior exposure to syphilis, which likely occurred decades earlier. The diagnosis may be missed if only the rapid plasma reagin (RPR) or VDRL test is checked because these tests are often negative in tertiary syphilis. In a series of 50 patients with a reactive fluorescent treponemal antibody absorption (FTA-ABS) test and eye findings consistent with active or inactive ocular syphilis (e.g., chorioretinitis, optic atrophy, iritis, interstitial keratitis), the average age was 59, and the VDRL test was reactive in only 24%.[74]

All patients with presumed ocular syphilis should have a lumbar puncture to exclude concomitant neurosyphilis, which may be present in 40% of patients.[74] Normal cerebrospinal fluid does not exclude ocular syphilis because ocular syphilis is frequently present without evidence of neurosyphilis. Patients who test positive for HIV have a higher rate of concurrent ocular syphilis and neurosyphilis.[73,75] All patients with ocular syphilis should be tested for HIV. In a study of 24 patients treated for ocular syphilis between 1998 and 2006, 11 patients were found to be HIV positive, and this was a new diagnosis in 7 patients.[76] HIV-positive patients are more likely than HIV-negative patients to have acute, bilateral uveitis with more extensive eye involvement (vitreous, retina, and optic nerve involvement simultaneously).[73,77]

It is likely that nearly all cases of uveitis and positive specific syphilis serologies represent infection with *Treponema pallidum* subsp. *pallidum*. It is possible, however, that some patients from areas endemic for yaws or bejel have positive serologies owing to exposure to these nonvenereal *T. pallidum* spp. in childhood but have uveitis from another etiology. Commercial laboratories often employ ELISA kits that use one or more cloned antigens or a lysate of the Nichols strain of *T. pallidum*. These kits vary in specificity and sensitivity, with false-positive results being common in low-risk populations. Additionally, some authors maintain that uveitis may be a late manifestation of yaws or bejel.[78–80] The eye findings they describe are similar to findings seen in ocular syphilis, and the diseases cannot be distinguished from syphilis serologically. The possible distinction would be important to the patient because of social implications, although it would not change therapy.

False-positive test results (e.g., low-titer RPR, rarely FTA-ABS) may also occur in patients with uveitis, especially as many have underlying rheumatologic conditions that increase the risk of a false-positive test. These are discussed later (see "Diagnosis").

Ocular Toxocariasis

Ocular toxocariasis usually affects children. It can be asymptomatic or cause unilateral decrease in vision. Although either dog *(Toxocara canis)* or cat *(Toxocara cati)* roundworms may cause ocular toxocariasis, *T. canis* is the more common etiology (see Chapter 290). A survey of ophthalmologists performed by the Centers for Disease Control and Prevention found that only 64% of patients with newly diagnosed ocular toxocariasis owned pets.[81] *Toxocara* infection occurs most commonly through ingestion of contaminated soil, and children exposed to playgrounds or sandboxes contaminated with dog or cat feces are at increased risk.[81]

There are three types of ocular manifestations: (1) peripheral chorioretinal granuloma (50% of cases), (2) posterior pole chorioretinal granuloma (25%), and (3) diffuse panuveitis (25%).[82,83] In nearly all cases, only one eye is involved. Diagnosis may be difficult, especially in panuveitis cases. Because the infection is confined to the eye, serology is often negative, and there is usually no peripheral eosinophilia or other signs of systemic parasitic infection. In addition, patients without ocular toxocariasis may have positive serologic tests due to incidental or past exposure to *Toxocara*. Data from the Third National Health and Nutrition Survey of a representative sample of the US population age 6 or older found that 13.9% were positive for *Toxocara* antibodies.[84] The diagnosis is often clinical, based on the appearance of the eye findings, particularly in an older child. A vitreous aspirate for evaluation of local *Toxocara* immunoglobulin G (IgG) compared with serum levels (Goldmann-Witmer coefficient) may be helpful in diagnosis.[85] However, vitreous aspiration is contraindicated in children in whom retinoblastoma is in the differential diagnosis.

In rare cases, ocular toxocariasis may be in the differential diagnosis of sporadic retinoblastoma. The distinction may be difficult, particularly in children older than 5 years of age in whom retinoblastoma is rare, but ocular toxocariasis is more common. All such cases should be evaluated by an experienced pediatric oncologic ophthalmologist because much of the distinction relies on the clinical examination. There are some clues in distinguishing retinoblastoma from ocular toxocariasis. The average age of unilateral cases of retinoblastoma is 2 years, and only 8% of retinoblastoma cases occur in children older than 5 years.[86] In contrast, ocular toxocariasis is typically seen in older children, with most cases occurring in children 4 to 8 years of age in some studies and even older in other studies. A retrospective study of ocular toxocariasis cases seen over 20 years in a uveitis center found that the average age was 16.5 years.[83] Another differentiating feature is that intraocular calcifications as seen on orbital ultrasound or computed tomography (CT) are characteristic of retinoblastoma but are not seen in ocular toxocariasis. Subtle findings on eye examination also help distinguish the entities. The presence of posterior synechiae and cataract argue against retinoblastoma and for chronic uveitis such as that caused by *Toxocara* or chronic endophthalmitis.[85] Both ocular

toxocariasis and retinoblastoma may have vitreous cells; however, these are WBCs in *Toxocara* infection. Shields and colleagues[86] at Wills Eye Hospital in Philadelphia described the vitreous cells in retinoblastoma as appearing different from WBCs—"soft and round, often appearing much larger and smoother in configuration than inflammatory cells." Diagnostic vitrectomy or aspirate must be avoided in cases of suspected retinoblastoma. Any instrumentation of the eye may spread the retinoblastoma to the orbit, and because of this risk, a child who undergoes vitreous aspirate for *Toxocara* diagnostic testing is committed to prophylactic chemotherapy if retinoblastoma is found instead. Orbital extension of retinoblastoma is the most significant factor predictive of eventual metastases and is associated with a very high mortality rate.[86]

Toxoplasmosis

Ocular toxoplasmosis is the most common infectious cause of posterior uveitis in the United States. Toxoplasmosis is a worldwide infection that may cause a majority of posterior uveitis cases in highly endemic areas such as Brazil and France. The characteristic funduscopic findings in ocular toxoplasmosis include a creamy yellow chorioretinal lesion adjacent to an old scar and marked vitreous inflammation. Ocular toxoplasmosis is discussed in detail in Chapter 290.

Tuberculosis

Ocular complications of systemic TB are rare. Ocular TB was diagnosed in only 1.4% of 10,524 patients seen in the eye clinic of a Boston sanatorium between 1940 and 1966.[87] A 1996 report of 1005 patients in India with active TB also found evidence of ocular disease in only 1.4%.[88] Ocular disease may be more common in HIV-positive patients with TB. A study of 100 patients hospitalized for TB in Madrid found presumed ocular TB in 24% of 45 HIV-positive patients compared with 13% in 55 HIV-negative patients.[89] Ocular TB was seen in 3.8% of HIV-positive patients with ocular lesions seen in a tertiary eye center in India; all had pulmonary TB as well. Patients presented with conjunctival involvement, subretinal abscess, choroidal tubercles, and panophthalmitis.

Ocular TB may manifest without evidence of systemic disease, so the diagnosis is often presumptive. Most patients have no history of TB, and half have normal chest radiographs.[90] Eye pathology is rarely available before vision is lost and the eye is enucleated. Biopsies of the uvea risk vision and are rarely performed. In a review of 40 cases with histologic evidence of intraocular TB reported between 1869 and 1991, only 1 case was proven by biopsy, and the rest were proven after loss of the eye.[91] Cultures of the aqueous or vitreous with rare exceptions are negative.[92] Diagnosis by PCR of aqueous or vitreous samples has been reported,[93,94] but the sensitivity and specificity of this test are unknown. Most reported PCR-positive cases have no culture confirmation, and many have no evidence of systemic disease.[92,93] A positive purified protein derivative (PPD) skin test or interferon-γ release assay blood test alone is of little help in determining if a patient with uveitis has ocular TB. In patients from TB-endemic countries, the incidence of latent TB is high (as is the incidence of active TB). It has been estimated that a patient with uveitis and a positive PPD test has only a 1% probability of having ocular TB.[95] Factors that make the diagnosis more likely include a history of TB or evidence of active disease, and the presence of eye findings typical of ocular TB such as multifocal choroiditis or granulomatous anterior uveitis.

Based on studies of patients with systemic TB and presumed ocular involvement, the spectrum of ocular findings has been described. TB can involve any part of the eye, but the most common finding is focal or multifocal choroiditis. Active or healed choroiditis was found in 78%[88] and 94%[89] of patients with systemic disease and presumed ocular TB in two reports. In earlier studies, choroidal involvement was seen in 30% to 40% of similar patients.[87] Choroidal *tubercles* are usually one-quarter to several disk diameters in size and are seen most often in the posterior pole rather than the periphery of the fundus. The number of lesions ranges from 1 to 60; however, most patients have fewer than 5.[91] One or both eyes may be involved. Lesions are yellow, white, or gray. In active disease, overlying vitreous inflammation may be present. Inactive choroidal lesions appear as scars. The appearance of choroiditis is not pathognomonic for TB, and similar lesions may be seen in sarcoidosis, syphilis, and, rarely, metastatic disease. The choroidal tubercles may coalesce and produce a type of uveitis called serpiginous-like choroiditis.[96] Chronic anterior uveitis, usually granulomatous (i.e., with mutton-fat keratic precipitates or iris nodules or both), is the next most common manifestation of ocular TB.[95] There may be an associated vitritis or choroiditis. A third common manifestation is retinal vasculitis or periphlebitis, often called Eales disease.[91] In 1880, Henry Eales, a British ophthalmologist, described recurrent retinal and vitreous hemorrhages in young men that he thought were immunologically mediated. The mechanism of Eales disease is still controversial, with some proponents arguing for direct infection of the retinal vessels and others for immune reaction to tuberculoprotein.[91] However, PCR studies of removed epiretinal membranes from eyes with Eales disease have demonstrated *Mycobacterium tuberculosis* genome in many cases, although cultures were negative.[97] Eales disease is most common in patients from India, Pakistan, and Afghanistan.[91] In India, 1 in 135 patients referred to a specialty eye center have Eales disease.[98] Typical features include vascular sheathing of retinal veins (periphlebitis), vitreous inflammation, and peripheral retinal capillary occlusion. Capillary occlusion leads to neovascularization and subsequent retinal hemorrhages (Fig. 115.5). The term *Eales disease* is sometimes used to refer to idiopathic occlusive retinal vasculitis rather than specifically to TB-related eye findings consistent with this. Whether most cases are associated with TB or respond to anti-TB therapy is unclear. A review of 500 patients with Eales disease seen in India in 1985–95 found that 95% were men, mean age was 30 years, 81% had bilateral eye involvement, and 97% had a positive Mantoux tuberculin skin test (of 360 patients tested).[99] The authors noted the high baseline prevalence of latent TB in India during the study period (70%–90%) and that only 15 patients of those evaluated by a pulmonary physician had evidence of active (nonocular) TB. Other manifestations of ocular TB include scleritis, interstitial keratitis, and optic neuritis.

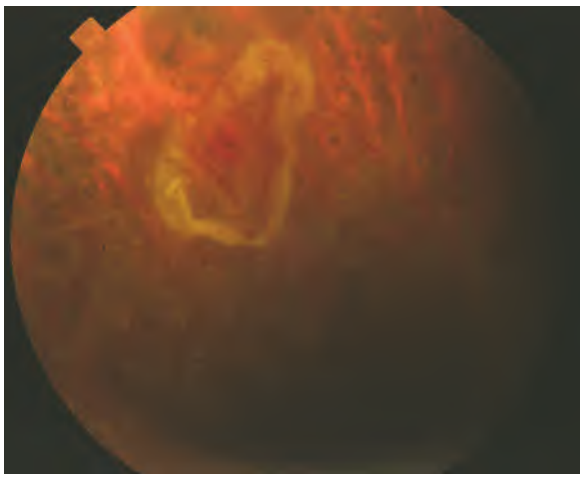

FIG. 115.5 Ocular tuberculosis. Retinal photograph showing signs of Eales disease in a patient from India: retinal neovascularization surrounded by a large yellow ring of fibrovascular proliferation in the vitreous. *(From Raizman MB, Haas JJ. Case 4: 1998. A 32-year-old man with vitreous hemorrhage and mediastinal lymphadenopathy. Case records of the Massachusetts General Hospital.* N Engl J Med. *1998;338:313–319.)*

West Nile Virus

The incidence of ocular involvement in West Nile virus (WNV) infection is unknown, but it may be common in patients with severe disease. The most common eye finding is multifocal chorioretinitis, and this is bilateral in nearly all cases. In an outbreak in Tunisia in 2003 involving 29 patients hospitalized with severe WNV, 80% had multifocal chorioretinitis, although 65% had no eye symptoms.[100] Retinal vasculitis was also common. Onset of lesions occurred 3 to 30 days after onset of acute illness. The ocular disease was self-limited, and chorioretinal lesions evolved into scars that resembled laser scars. A report of seven patients with WNV in the United States also found that bilateral multifocal

chorioretinitis was the most common finding, occurring in 86% of eyes.[101] Other findings included retinal hemorrhages, chorioretinal streaks, vitritis, retinal vasculitis, and optic atrophy. A majority of patients in both studies were diabetic. Outcomes were good in most cases, although the few patients with optic atrophy or occlusive retinal vasculitis had permanent loss of vision.

WNV may also produce retinal findings in some birds. A study of 13 hawks with naturally acquired WNV infection found that all had similar funduscopic findings, with exudative chorioretinal lesions or scars in a linear or geographic pattern.[102]

Whipple Disease

Whipple disease is rare, and ocular findings are even more so. Bilateral granulomatous panuveitis in one patient has been described. This patient had iris and retinal nodules as well as vitritis and a chronic course over 4 years before diagnosis.[103] A case of Whipple disease in a patient with a long-standing renal transplant included findings of bilateral vitritis and chorioretinitis.[104] A review of 11 patients with ocular Whipple disease found that chronic uveitis was the most common manifestation, affecting 9 patients, whereas 1 patient had isolated bilateral disk swelling and 1 had Parinaud syndrome.[105]

Zika Virus

Zika is a flavivirus infection transmitted by mosquito bites, largely *A. aegypti*, and was originally seen in Africa and Asia. Zika was first described in the Western Hemisphere in 2015, when an epidemic began in Brazil, rapidly spreading throughout the country. Zika is currently a risk in multiple parts of the world including Central and South America, Mexico, the Caribbean, and parts of Asia and Africa (see Chapter 153). Affected adults may experience a nonpurulent conjunctivitis or anterior uveitis,[106] whereas infants infected in utero may have a broad spectrum of retinal and optic disk findings.[25] Retinal findings are very rare in adults. An eye center in Florida reported bilateral chorioretinitis (diffuse, confluent, placoid, and multifocal lesions) in an immunocompromised woman from Puerto Rico who was undergoing chemotherapy for lymphoma.[106] The chorioretinal lesions spontaneously resolved over the following 5 months.

ENDOPHTHALMITIS MIMICKING UVEITIS

Endophthalmitis usually manifests acutely, but two types that usually have a subacute or chronic presentation may mimic, and be initially misdiagnosed as, uveitis. These are discussed next and detailed in Chapter 114.

Chronic Postcataract Endophthalmitis

Patients with a history of several months of unilateral anterior chamber inflammation following cataract surgery in the same eye should be suspected of having chronic pseudophakic endophthalmitis rather than anterior uveitis. Nearly all such cases are due to *Propionibacterium acnes*. Clues to the diagnosis include the history of onset after cataract surgery and the finding on eye examination of white plaques in the posterior lens capsule. Aqueous or vitreous cultures are usually negative. Chronic postoperative endophthalmitis may also be due to fungi, as discussed next.

Chronic Endophthalmitis Due to Fungi

By convention, intraocular inflammation due to fungi is considered endophthalmitis rather than uveitis. Chronic endophthalmitis due to fungi may occur postoperatively or following seeding of the eye during occult fungemia (endogenous fungal endophthalmitis) and may be initially mistaken for a noninfectious uveitis. Examination of the eye may reveal findings that suggest the diagnosis of fungal endophthalmitis, however. These findings include a "clumped" appearance of inflammation in the aqueous humor in post-cataract surgery cases, for example, or fluffy white lesions in the vitreous or on the retina in endogenous endophthalmitis cases. In cases due to occult fungemia, the patient's medical history also may provide clues that suggest a fungal etiology, such as risk factors for candidemia (e.g., intravenous drug abuse or a recent indwelling central venous catheter) or risk factors for fungemia due to molds (e.g., immunocompromise from organ transplantation or chemotherapy, or recent intravenous drug abuse). Fungal endophthalmitis is discussed further in Chapter 114.

DIAGNOSIS OF INFECTIOUS UVEITIS

Patients with infectious uveitis often present a diagnostic dilemma to ophthalmologists and infectious diseases physicians. The diagnosis is nearly always made clinically, primarily on the basis of the eye examination by the ophthalmologist. Ophthalmologists do not need to refer cases with typical eye findings (e.g., classic *Toxoplasma* chorioretinitis) to infectious diseases physicians, so the infectious disease specialist sees only cases that have atypical features or are rapidly progressive. The diagnosis often cannot be proven by studies on the aqueous or vitreous, and these are the parts of the eye that can be sampled relatively safely, although vitreous sampling has some risk.

Approach to the Patient With Uveitis

An infectious diseases physician consulting on a case of uveitis should (1) obtain a copy of the ophthalmologist's notes for review (see Chapter 111 for help with interpretation of these notes); (2) determine what anatomic category of uveitis is involved—that is, anterior, intermediate, posterior, or panuveitis; and (3) ask the ophthalmologist what his or her differential diagnosis is based on the findings of the eye examination alone. The anatomic category limits the likely infectious and noninfectious etiologies, as does the pace of the infection. The anatomic category is determined by the ophthalmologist based on the site of greatest inflammation.

Pathology of vitreous samples is important in establishing a diagnosis of ocular lymphoma, and intraocular cultures are essential in cases of "uveitis" due to chronic *Candida* or *P. acnes* endophthalmitis. Molecular diagnostic techniques such as PCR have been helpful in viral retinitis, but the sensitivity appears to be low in other types of uveitis. The technique for sampling aqueous or vitreous is discussed in Chapter 111.

PCR has proven most useful in herpetic uveitis cases, such as herpetic anterior uveitis and ARN. The aqueous or vitreous may be tested for HSV, VZV, or CMV. Yamamoto and coworkers[107] found that PCR tests of aqueous samples from 7 patients with recurrent iridocyclitis of suspected viral etiology were positive for either HSV (6 samples) or VZV (1 sample), whereas samples from 17 control eyes were negative. A retrospective study from Florida of 53 patients with anterior uveitis found PCR of the aqueous humor to be positive for HSV in 8% (4 of 49), VZV in 3% (1 of 35), and CMV in 2% (1 of 47).[108] In a study of 28 patients with ARN, PCR was positive in 27 (96%) for HSV, VZV, or CMV.[109] Another study using PCR of aqueous in ARN or PORN diagnosed these viruses in 86% of cases.[110] A study of 433 PCR tests of 133 patients with possible infectious chorioretinitis, analyzed for HSV, VZV, CMV, EBV, and toxoplasmosis, identified 81% of the 95 patients with a final clinical diagnosis of infectious uveitis.[111]

The sensitivity and specificity of aqueous or vitreous PCR for most other types of uveitis are not yet known, although sensitivity appears to be low enough that a particular etiology should not be excluded from the differential diagnosis based on a negative PCR result. The gold standard is usually clinical diagnosis or response to therapy or both because most agents of uveitis cannot be cultured. In a study from France that included 55 patients with clinically diagnosed ocular toxoplasmosis who also underwent vitreous sampling, the sensitivity of PCR was only 27%, although specificity was 100%.[112] Similarly, in a series of 9 patients with ocular Whipple disease who underwent vitreous sampling, all had periodic acid–Schiff–positive macrophages, but the sensitivity of vitreous PCR was only 60% (3 of 5 tested).[107] For ocular TB, both false-positive and false-negative PCR results have been described. Gupta and colleagues[94] reported that 10 of 17 patients (60%) with presumed ocular TB had positive aqueous PCR assays for *M. tuberculosis,* with the clinical diagnosis based on a positive PPD test or abnormal chest radiograph or both plus the absence of another uveitis diagnosis. However, PCR was also positive in 23% of the control group of patients with uveitis who had a negative PPD test and normal chest radiograph. False-negative PCR tests may also occur in some PCR assays because aqueous and vitreous specimens may contain inhibitors.[113]

Positive serologic tests such as IgG antibodies to *Toxoplasma,* HSV, VZV, or CMV also may be of little help given the high prevalence of

such antibodies in the general population. However, negative serologies to these pathogens may be helpful and may effectively exclude these diagnoses in the appropriate clinical setting. A specific treponemal test for syphilis (e.g., *T. pallidum* particle agglutination or FTA-ABS test) should be ordered on all patients with uveitis. If this test is positive and eye findings are consistent with ocular syphilis, the patient should be treated for ocular syphilis with high-dose intravenous penicillin. It is possible that the positive specific test for syphilis represents an incidental finding and that the uveitis has another etiology, but patients require treatment for the possibility of syphilitic uveitis because it is nearly impossible to exclude. Syphilis can produce almost any ocular manifestation.[114] Such patients should also have a lumbar puncture, but a normal cerebrospinal fluid profile will not exclude the diagnosis of ocular syphilis. The *T. pallidum* particle agglutination assay (TPPA) is preferred because the FTA-ABS test may be falsely positive in some patients, especially patients with rheumatologic conditions.[115] RPR also should be checked, although false-positive tests are common in autoimmune conditions, and all positive RPR tests must be confirmed with a specific treponemal test. A negative RPR test does not exclude ocular syphilis because it may be negative in tertiary syphilis; these RPR-negative, presumed ocular syphilis cases typically have an indolent presentation. Fulminant cases of syphilitic uveitis, characterized by marked intraocular inflammation, are nearly always due to secondary syphilis, and in these cases, the RPR titer is usually high. Treatment for presumed syphilis should be started immediately in these fulminant cases and not delayed until confirmatory specific treponemal test results return.

For both medical and social reasons, it is important to determine that a positive syphilis serologic test is not falsely positive. Although it is well known that nontreponemal tests such as RPR may be falsely positive in a variety of patient populations, the FTA-ABS test may be falsely positive as well, particularly in patients with rheumatologic conditions. A prospective cohort study of 50 patients with rheumatologic conditions and at least one serologic test positive for syphilis found that the specificity of the FTA-ABS test was only 68% in this population.[115] In addition, FTA-ABS may be falsely positive in patients with Lyme disease. ELISA tests for syphilis have also been plagued with false-positive results as well as variability among laboratories. Commercial laboratories often use ELISA kits that employ one or more cloned antigens or a lysate of the Nichols strain of *T. pallidum*. These kits vary a great deal in specificity and sensitivity. Any patient with uveitis and a positive FTA-ABS test should have confirmation with a *T. pallidum* particle agglutination assay (TPPA) or enzyme immunoassay. Because results from these confirmatory tests may take more than a week, therapy for possible ocular syphilis should be started as soon as the diagnosis is suspected if delay in therapy could compromise vision.

Radiologic studies of the eye or orbit are sometimes helpful in uveitis, but primarily for evaluation of noninfectious etiologies. Magnetic resonance imaging of the brain and orbit may be helpful in suspected cases of ocular-CNS lymphoma if brain lesions are found, although eye disease may precede CNS lesions by months. Fluorescein angiography of the eye may show retinal vascular patterns consistent with certain diseases such as viral-induced vasculitis in CMV. Indocyanine green angiography of the eye was found to be useful in detecting and following subclinical choroidal lesions in eight patients with presumed ocular TB.[116] Chest CT may be helpful in distinguishing sarcoidosis from TB in patients with granulomatous uveitis because these diseases often produce similar eye findings. In a study of 50 patients with uveitis suspected to have ocular sarcoidosis, CT was positive for sarcoidosis in 20%, although none of the patients had pulmonary symptoms.[117]

THERAPY

Acute anterior uveitis due to HSV is treated with topical corticosteroids and oral acyclovir or valacyclovir. Long-term prophylactic oral acyclovir (400 mg twice daily) seems to be beneficial in preventing recurrences of herpetic stromal keratitis[118] and anterior uveitis.[119]

ARN due to HSV or VZV is usually treated with high-dose intravenous acyclovir (10 mg/kg every 8 hours in patients with normal renal function) for 1 to 2 weeks followed by valacyclovir or famciclovir for 6 weeks to several months.[11,120] The optimal duration is unknown. For severe cases, intravenous acyclovir for 1 to 2 weeks followed by valacyclovir, 1 to 2 g every 8 hours, for several weeks is often given and may be followed by several months of oral acyclovir, 400 mg twice daily. Intravitreal injections of foscarnet are also typically given in severe cases. More recently, oral valacyclovir usually given at 2 g every 8 hours (twice the standard dose) has been favored by many ophthalmologists in initial treatment of ARN. A retrospective review of 62 patients with ARN (90% unilateral) treated between 1992 and 2016 at a specialty hospital in London with either intravenous acyclovir (33 patients) or oral valganciclovir (29 patients) found no difference in visual outcome, although only one-third of patients had a good visual outcome.[119] In immunocompromised patients presenting with ARN, CMV could be an etiology, and treatment with intravenous ganciclovir should be given instead of acyclovir until or unless CMV can be excluded (e.g., seronegative patients). Retinitis can progress rapidly (within 24 hours) in ARN, and the goal of initial therapy in ARN is to halt progression of retinitis and prevent involvement of the other eye. The infectious diseases physician should work with the retina specialist on a daily basis to determine if retinitis is progressing despite intravenous acyclovir. If retinitis is worsening despite therapy, an empirical switch to intravenous foscarnet should be considered as well as intravitreal injections of foscarnet. Cases of ARN in immunocompetent hosts that progressed despite intravenous acyclovir have responded to combination therapy with intravitreal ganciclovir or foscarnet injections plus systemic ganciclovir, foscarnet, or cidofovir.[121–123] Repeated intravitreal foscarnet injections may be required. Intravitreal foscarnet may reduce the rate of retinal detachment, a common complication of ARN, particularly VZV ARN.[124] VZV ARN tends to be more severe and progress more rapidly than HSV ARN.[124] For any type of ARN, because retinitis may occur in the second eye several months after onset of ARN in the first eye, oral antiviral therapy (e.g., acyclovir, valacyclovir, famciclovir) is often continued for several months following initial intravenous therapy. For immunosuppressed patients, suppressive antiviral therapy should probably be given for the duration of immunosuppression, which may be indefinite in many cases.

PORN has a dismal outcome despite therapy in most cases. In countries where resources are limited, treatment may be especially difficult. A center in South Africa used outpatient treatment with repeated intravitreal injections of ganciclovir over weeks to months (median, 12 injections) in 50 eyes of HIV-positive patients with PORN, and only 13% of eyes lost all vision (no light perception) compared with 60% in earlier published studies.[125] The best outcomes have been reported in case reports and small series using intravitreal and systemic antiviral therapies. The importance of starting antiretroviral therapy in patients not already receiving this has also been emphasized. There have been successes with repeated intravitreal injections with foscarnet and ganciclovir, in addition to prolonged combination intravenous therapy with these agents and the initiation of antiretroviral therapy in HIV-positive patients. In one patient with bilateral PORN, vision was lost in one eye, but an aggressive treatment led to visual recovery in the other eye.[126] This treatment included intravenous foscarnet and ganciclovir for 7 months and concurrent nearly twice-weekly intravitreal injections with foscarnet, 1.2 mg/0.05 mL, and ganciclovir, 2 mg/0.05 mL (total 58 injections over 6 months). Antiretroviral therapy was also initiated, and anti-VZV therapy was stopped when $CD4^+$ T-cell count increased to 100 cells/mm^3. The patient maintained 20/20 vision in the treated eye 2 years later.

Ocular syphilis should be treated the same as neurosyphilis, with 10 to 14 days of intravenous penicillin (3 to 4 million U every 4 hours in patients with normal renal function). A short course of systemic corticosteroids (e.g., oral prednisone, 60–80 mg daily) may be required during the initial few days of penicillin therapy to decrease intraocular inflammation rapidly in patients presenting with marked intraocular inflammation. Many experts follow intravenous penicillin with injections of 2.4 million U of intramuscular benzathine penicillin once weekly for 3 weeks. All patients with presumed ocular syphilis should be tested for HIV. All patients should have a lumbar puncture to exclude concurrent neurosyphilis before starting intravenous penicillin, if possible. However, in acute cases with vision-threatening uveitis, therapy should not be delayed if a lumbar puncture cannot be performed in a timely way. The reason for performing a lumbar puncture is to determine if there is

concurrent neurosyphilis (i.e., with CNS involvement) because such patients will require a follow-up lumbar puncture at 6 months to document resolution of infection.

Ocular TB should be treated with the same medications and duration of therapy as TB meningitis, although ethambutol is avoided if possible because of potential ocular toxicity. A short course of systemic corticosteroids may be necessary initially if there is sight-threatening inflammation.

The treatment of CMV retinitis is discussed in Chapter 137, the treatment of ocular toxoplasmosis is discussed in Chapter 278, and the treatment of ocular toxocariasis is discussed in Chapter 290. Treatment of Lyme uveitis should be the same as for neuroborreliosis, preferably with intravenous ceftriaxone. Chronic endophthalmitis due to *P. acnes* or *Candida* is discussed in Chapter 114.

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116 Periocular Infections

Marlene L. Durand

SHORT VIEW SUMMARY

Definition
- Periocular infections include infections of the eyelids, lacrimal system, and orbit.
- Eyelid infections include hordeolum, stye, blepharitis, and superinfected chalazion.
- Lacrimal system infections include dacryoadenitis (infection of the lacrimal gland), canaliculitis (infection of the canaliculi that collect tears in the medial canthus and drain into the lacrimal sac), and dacryocystitis (infection of the lacrimal sac).
- Preseptal cellulitis involves the soft tissues in front of the orbital septum. The orbital septum comprises fibrous tissue that extends from the orbital rim into the tarsal plate of the lids.
- Orbital infections include orbital cellulitis, subperiosteal abscess, and orbital abscess. These may lead to cavernous sinus thrombophlebitis.

Microbiology
- Lid infections: *Staphylococcus aureus,* streptococci
- Dacryoadenitis: In acute cases, *S. aureus,* streptococci, rarely *Haemophilus influenzae,* Epstein-Barr virus, and herpes zoster. Most chronic cases are noninfectious, but *Mycobacterium tuberculosis* is an infectious cause.
- Canaliculitis: *Actinomyces israelii,* also staphylococci, streptococci in primary infections; in patients with punctal plugs, unusual organisms (e.g., *Pseudomonas, Mycobacterium chelonae*) may be the pathogen.
- Dacryocystitis: *S. aureus,* streptococci; also gram-negative bacilli, anaerobes
- Preseptal cellulitis: *S. aureus* or streptococci in localized infections. Preseptal cellulitis rarely may result from bacteremia due to *H. influenzae,* group A streptococci, or *Streptococcus pneumoniae.*
- Orbital infections: *S. aureus,* including methicillin-resistant *S. aureus, Streptococcus anginosus (milleri),* other streptococci (including *S. pneumoniae), H. influenzae,* other gram-negative bacilli, anaerobes. Mixed infections are common.

Diagnosis
- Clinical examination in lid infections and lacrimal system infections.
- Preseptal cellulitis must be distinguished from orbital infections (orbital cellulitis, subperiosteal and orbital abscess). Orbital infections almost always have one or more of the following "orbital" findings: proptosis, which may not be grossly apparent but can be measured as 2 mm or more difference in the Hertel exophthalmometer measurements; ophthalmoplegia; and decreased vision. Preseptal cellulitis has none of these features, only lid edema and erythema. Computed tomography (CT) scan should be performed on any patient with orbital findings. CT should be considered in children who present with what appears to be severe preseptal cellulitis because they may have subperiosteal abscess (see text).

Therapy
- Varies by diagnosis; see text.
- Orbital infections are much more serious than preseptal cellulitis, and all orbital infections must be treated with intravenous antibiotics. Subperiosteal abscesses usually require surgical drainage, and orbital abscesses almost always do. Drainage of an adjacent infected sinus may be indicated.

Periocular infections include infections of the eyelids, lacrimal system, and orbital soft tissues that surround the globe of the eye. These infections may affect vision if not recognized and treated appropriately.

EYELID INFECTIONS

Anatomy

Each eyelid contains a fibrous tarsal plate that gives the lid its firmness (Fig. 116.1). Within each tarsal plate are 20 to 25 meibomian (or tarsal) glands (Fig. 116.2). These glands may be seen as faint yellow lines on the inner surface of the everted lid, extending perpendicular to the lid margin. Meibomian glands are sebaceous glands that secrete sebum, an oily substance. Sebum prevents the tear film from evaporating too quickly from the ocular surface. At the lid margin, adjacent to the eyelash follicles, are smaller sebaceous glands called *glands of Zeis.*

Hordeolum

A hordeolum is an acute infection of a sebaceous gland of the lid, usually caused by *Staphylococcus aureus.* An internal hordeolum is an infection of a meibomian gland, and patients present with lid swelling, erythema, and tenderness. Internal hordeola may point toward either the skin or the conjunctival surface. An external hordeolum (stye) is an infection of a gland of Zeis, and patients present with a painful pustule that points to the lid margin. Internal and external hordeola usually respond to frequent warm compresses. Topical bacitracin or erythromycin ointment may be used at night. Incision and drainage of the lesion is rarely required. There have been no randomized studies of the various medical treatments commonly prescribed for acute internal hordeola (e.g., warm compresses, antibiotics, lid scrubs), so the effectiveness of various treatments is unknown.[1] Methicillin-resistant *Staphylococcus aureus* (MRSA) may play a role in some cases.[2]

Chalazion

A chalazion is a sterile granulomatous reaction to inspissated sebum within an obstructed meibomian gland. It may result from an internal hordeolum or arise de novo.[3] Patients present with a nontender nodule within the lid that points to the conjunctival surface. Chalazia may become large and press on the ocular surface, distorting vision. Most chalazia resolve within 1 month, but recurrences are common in patients with chronic blepharitis. A randomized prospective trial treating patients with primary chalazia that had persisted for at least 1 month, despite conservative measures, found that intralesional triamcinolone injection was as effective as incision and curettage.[4] A three-way randomized trial comparing 4 to 6 weeks of hot compresses alone versus hot compresses plus either topical tobramycin or topical tobramycin-dexamethasone found that complete resolution occurred in only 18% of patients, and there was no significant difference between the groups.[5] Lesions with a lower pretreatment duration were more likely to resolve completely. Acute superinfection of a chalazion may occur, which should be treated with antibiotics (Fig. 116.3). Persistent or recurrent chalazia should be biopsied to exclude sebaceous cell carcinoma of the lid.

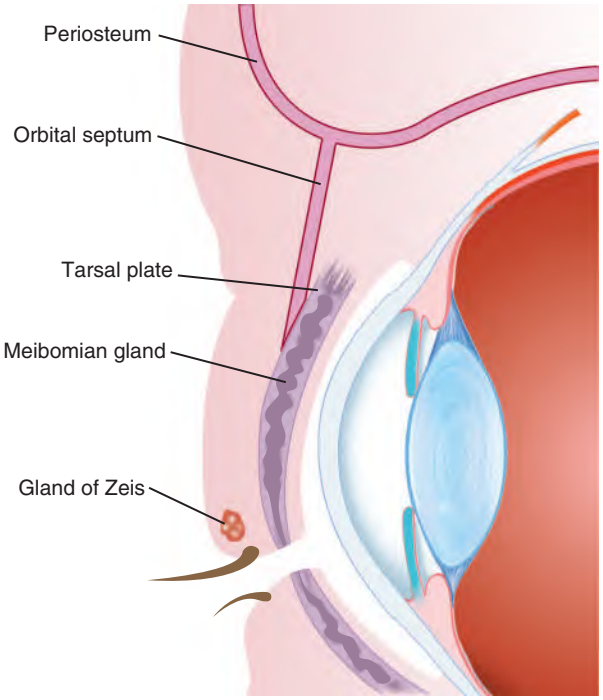

FIG. 116.1 Diagram of the anterior portion of the eye and orbit, illustrating the orbital septum and tarsal plate of the eyelid. Infections anterior to the orbital septum are described as preseptal, whereas infections posterior to the septum are considered orbital. Meibomian glands lie within the tarsal plate.

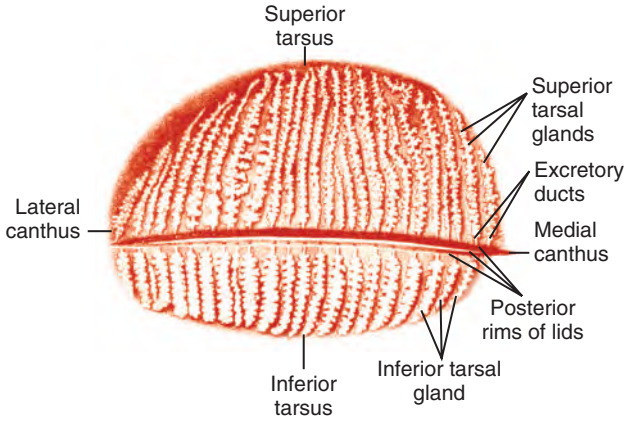

FIG. 116.2 The meibomian glands. *(From Warwick RE.* Wolff's Anatomy of the Eye and Orbit. *Philadelphia: Saunders; 1976.)*

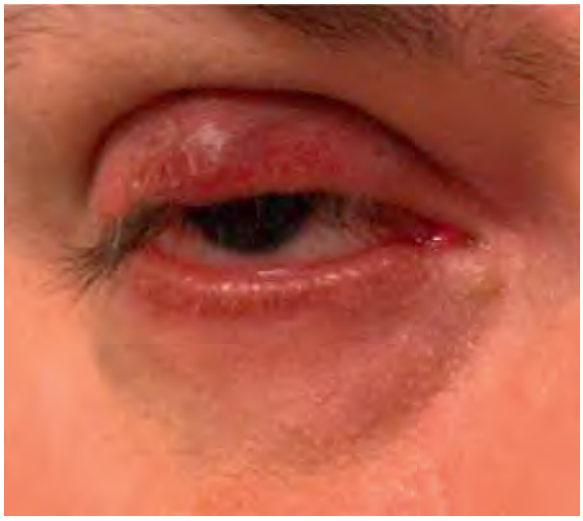

FIG. 116.3 Superinfected chalazion.

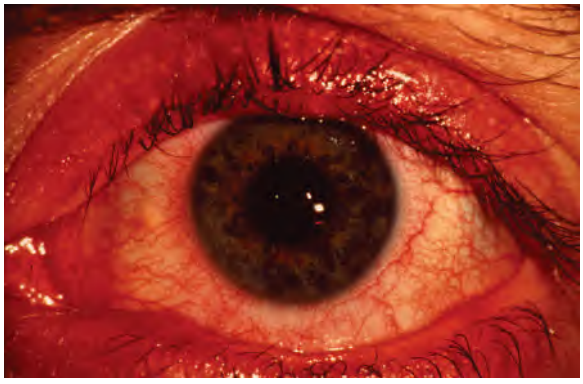

FIG. 116.4 Photograph of eyelids with marginal blepharitis.

Blepharitis

Blepharitis (Fig. 116.4) is an inflammation of the eyelids, usually involving the lid margins. It is one of the most common conditions seen by ophthalmologists. Blepharitis is usually chronic and may lead to ocular surface disease, such as chronic conjunctivitis, functional tear deficiency, and corneal inflammation or infection (keratitis). The American Academy of Ophthalmology classifies blepharitis as either anterior or posterior, with anterior blepharitis involving the lid skin, base of eyelashes, and eyelash follicles, whereas posterior blepharitis involves the meibomian glands.[6] Anterior blepharitis is further categorized as either "staphylococcal" or seborrheic. There is significant overlap in symptoms between categories. Patients with scaling, crusting, erythema of lid margins are considered to have staphylococcal blepharitis, although evidence for a role of staphylococci is minimal, and supporting studies are older than 30 years.[6] Patients with seborrheic blepharitis have greasy scaling of the eyelids and usually also of eyebrows and scalp. Patients with meibomian gland dysfunction typically have thickened lid margins with pouting or plugged meibomian orifices, and the meibomian secretions expressed by gentle massage of the lids ranges from turbid fluid to thick, cheesy material.[6] Rosacea and seborrheic dermatitis are often present in patients with meibomian gland dysfunction. Treatment of chronic blepharitis is usually with twice-daily gentle eyelid scrubs using either diluted baby shampoo or a dedicated commercial eyelid cleanser; a recent study found the latter to be superior.[7] A topical antibiotic ointment (e.g., bacitracin) applied to the lid margins may be helpful in cases with acute inflammation. Oral tetracycline may be helpful if there is associated rosacea. Cultures of eyelid margins are not routinely performed but may be useful in some cases because, rarely, cases may be due to unexpected bacterial or fungal pathogens.[8] Phthiriasis palpebrarum is infestation of the eyelashes by crab lice. Patients have pruritus of the lid margins and blepharoconjunctivitis and are often initially misdiagnosed as having an allergic or atopic condition. The lice, which burrow into the lid margin, may be difficult to see.[9] Herpes simplex blepharitis has been described in adults and children, may be recurrent, and is occasionally bilateral.[10,11] Blastomycosis is a rare cause of a granulomatous blepharitis (Fig. 116.5). *Demodex* mites are common ectoparasites of the skin and may infest the lid margins; infestation is associated with cylindrical dandruff around the lashes. *Demodex folliculorum* can be found in the lash follicle and *Demodex brevis* in sebaceous and meibomian glands.[12] The possible association between *Demodex* and chronic blepharitis was first postulated 50 years ago.[13] Studies of topical treatments have found that lid scrubs with tea tree oil (from the leaf of the tree *Melaleuca alternifolia*) are effective in eradicating *Demodex,*[14] and such scrubs have effectively treated some cases of chronic blepharitis.[12] A case of chronic blepharitis that mimicked sebaceous gland carcinoma

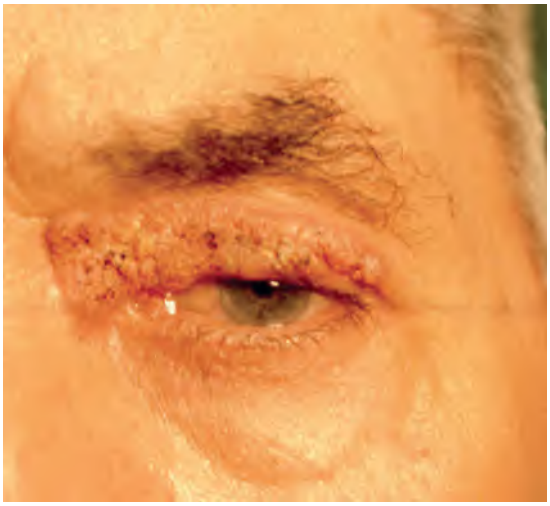

FIG. 116.5 Blastomycosis involving the eyelid in an otherwise healthy man with a normal chest radiograph. *(Courtesy Dr. John Bennett.)*

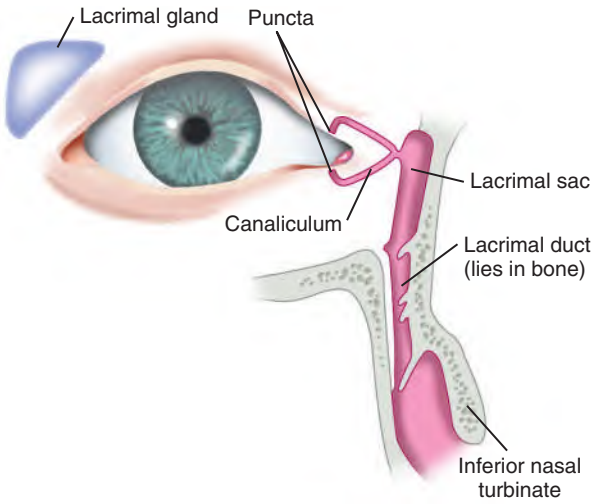

FIG. 116.6 The lacrimal system.

was found to be due to *Demodex* on lid biopsy and responded to tea tree oil lid scrubs.[15]

INFECTIONS OF THE LACRIMAL SYSTEM

Anatomy

The lacrimal gland is located beneath the upper outer orbital rim (Fig. 116.6). It produces tears that flow across the eye and then drain through the puncta, canaliculi, lacrimal sac, and lacrimal duct into the nasal cavity. The only parts of the lacrimal system that are visible on examination are the puncta and sometimes the lacrimal gland. The size of the lacrimal gland varies, but a portion may be visible in some patients when the upper lid is everted and the patient looks down and in. The gland then appears as a pink mass under the conjunctiva, just under the lateral part of the upper orbital rim.

Dacryoadenitis

Dacryoadenitis is an inflammation of the lacrimal gland. Infections are rare and may be acute or chronic. Patients with acute dacryoadenitis present with a tender area of erythema and swelling in the lateral part of the upper lid. Acute dacryoadenitis may lead to preseptal or orbital cellulitis or may suppurate into an abscess[16]; *S. aureus* and streptococci are common pathogens. A series of 11 cases reported *S. aureus* in more than half (6 cases), followed by *Streptococcus pneumoniae* (2), mixed skin flora (2), and *Haemophilus influenzae* (1).[17] There are case reports of acute suppurative dacryoadenitis due to *Pseudomonas,* brucellosis, and cysticercosis.[18–20] Epstein-Barr virus may cause acute nonsuppurative dacryoadenitis in mononucleosis, which may be unilateral or bilateral.[21,22] Herpes zoster has been the cause of acute dacryoadenitis that preceded (by 2 days) the onset of a vesicular rash in the first division of the trigeminal nerve.[23,24] A study found that dacryoadenitis was present in one-third of patients with *Acanthamoeba* keratitis, although direct infection of the lacrimal gland was not found.[25] Chronic infectious dacryoadenitis is rare, but most reports describe *Mycobacterium tuberculosis* as the cause.[26,27] Most cases of chronic dacryoadenitis are inflammatory rather than infectious, however. Sjögren disease and sarcoidosis are the most common associated diseases, although cases of Crohn's disease and granulomatosis with polyangiitis presenting as chronic dacryoadenitis have been described.[28,29] Granulomatous inflammation of bilateral lacrimal glands was seen in one patient receiving interferon-α and ribavirin for hepatitis C; evaluation for sarcoidosis was negative.[30] Thyroid orbitopathy may rarely present with lacrimal gland enlargement.[31] Tumors are an important cause of lacrimal gland enlargement, and dacryoadenitis has been a presenting sign in rare cases of lymphoma and leukemia.[32]

Canaliculitis

Canaliculitis may occur spontaneously or develop after placement of a silicone or temperature-sensitive acrylic polymer punctal plug in the canaliculi. These plugs are used to treat dry eyes, and canaliculitis results in approximately 8% of patients with long-term follow-up.[33] Symptoms of canaliculitis include tearing and irritation in the medial portion of the affected eyelid, and examination reveals a swollen, "pouting" punctum and erythema of the adjacent nasal conjunctiva. There may be a unilateral discharge and conjunctivitis. The lower canaliculus is affected more often than the upper. A yellow-green exudate and yellowish concretions may be expressed from the involved punctum in many cases. The concretions, called *sulfur granules,* are formed by *Actinomyces israelii,* the organism in the majority of cases.[34] A literature review of 188 reported cases found that the major organisms were *Actinomyces* (30%), streptococci (12%), and staphylococci (10%).[35] The most common pathogen may differ depending on region and whether the canaliculitis is primary or secondary to punctal plugs. In a series from India of 74 patients with primary canaliculitis, staphylococci were the major organisms (39%),[36] whereas in a series from Taiwan of 76 patients with canaliculitis, streptococci (28%) were most common in primary canaliculitis and *Pseudomonas* (46%) in plug-related canaliculitis.[37] Various other organisms have been reported, including *Mycobacterium chelonae* (in several plug-related infections),[38] *Eikenella corrodens,* and *Streptococcus anginosus (milleri)* group,[39] *Arcanobacterium haemolyticum,*[40] *Citrobacter freundii,*[41] *Aggregatibacter aphrophylus*,[42] and *Nocardia asteroides*. Treatment of canaliculitis requires removal of canalicular material and concretions and removal of a punctal plug if present. After this, topical antibiotics are usually given.[37] On occasion, surgical exploration is required.

Dacryocystitis

Dacryocystitis, or inflammation of the lacrimal sac, is the most common infection of the lacrimal system. It arises because of obstruction of the lacrimal duct, pooling of tears in the lacrimal sac, and subsequent infection. Obstruction may be congenital or may result from trauma, tumors, infection, or inflammation of the duct. Acute dacryocystitis symptoms include pain, swelling, and erythema near the nasal corner of the eye (Fig. 116.7). There is usually epiphora (excessive tearing) and a purulent discharge. Infants often have lacrimal duct obstruction with epiphora, but acute dacryocystitis rarely complicates the obstruction. The most common causes of acute dacryocystitis are *S. aureus* and streptococci, but gram-negative bacilli also play a role. One series of 137 patients found that *Pseudomonas* (12%) was the second most common pathogen after *S. aureus* (30%).[43] Treatment requires antibiotic therapy (e.g., ampicillin-sulbactam) and usually incision and drainage of a lacrimal sac abscess. In one study, incision and drainage was an outpatient procedure requiring only local anesthesia in approximately 80% of cases.[44] A repeat drainage procedure was required within 1 month in 8%. Chronic or recurrent dacryocystitis usually requires a surgical procedure, dacryocystorhinostomy (DCR). Cultures taken when purulence was found at the time of DCR surgery in one series were

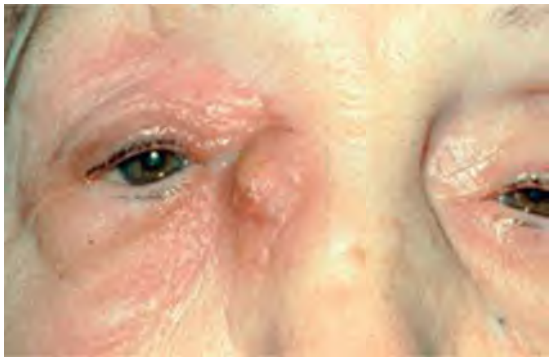

FIG. 116.7 Acute dacryocystitis. *(From Durand ML. Periocular infections. In: Schlossberg D, ed.* Clinical Infectious Disease. *2nd ed. Cambridge, UK: Cambridge University Press; 2015:117.)*

polymicrobial in 40%, and the most frequent pathogens were *S. aureus* (20%), streptococci (12%), and gram-negative bacilli (56%), with *H. influenzae* (20%) the most common gram-negative organism.[45] Another study also found that *H. influenzae* was the predominant gram-negative bacillus recovered.[46] Anaerobes were found in 19% in that study. Fungi are very rare causes of dacryocystitis, but a case of mucormycosis involving the lacrimal sac has been described.[47] *Rhinosporidium seeberi,* an aquatic protistan parasite seen especially in tropical climates, such as southern India, may cause chronic dacryocystitis. A report from India described 50 patients with ocular rhinosporidiosis over a 2.5-year period, including 26% with lacrimal sac involvement.[48] Bloody discharge from the puncta was a feature of lacrimal sac infection, and at surgery, a pink, vascularized growth was found in the lacrimal sac.

Patients with an episode of acute dacryocystitis and who do not ultimately undergo a DCR procedure may have further episodes of acute dacryocystitis. One study found this risk was 25%.[44]

PRESEPTAL CELLULITIS AND ORBITAL INFECTIONS

Anatomy

The orbital septum is a thin, fibrous membrane that serves as a barrier between the superficial lids and the orbit. The septum arises from the orbital periosteum at the orbital rim and extends to the tarsal plates of the eyelids (see Fig. 116.1). Infections anterior to the septum are preseptal, and infections posterior to the septum are orbital. *Preseptal cellulitis* involves only the lids and not the orbit, whereas *orbital cellulitis* involves the soft tissues (fat, muscle) contained within the bony orbit (Fig. 116.8). The bony orbit is shaped like a cone placed horizontally, apex tilted medially. It is surrounded by the paranasal sinuses for much of its circumference: the frontal sinus superiorly, the maxillary sinus inferiorly, and the ethmoid medially. The floor of the frontal sinus is also the roof of the orbit. The medial orbital wall, the paper-thin lamina papyracea, is also the lateral wall of the ethmoid sinus. It contains multiple foramina for nerves and blood vessels, and some people also have natural defects called *Zuckerkandl dehiscences.* For these anatomic reasons, ethmoid sinusitis is the most common cause of sinus-related orbital infection. Periosteum (periorbita) lines the orbit, and infection from the ethmoid sinus may cross the lamina papyracea and collect beneath the medial periorbita as a *subperiosteal abscess*. An *orbital abscess* may result from sinusitis without antecedent subperiosteal abscess or orbital cellulitis. The venous drainage of the middle third of the face and paranasal sinuses is primarily through the orbital veins, which drain inferiorly to the pterygoid plexus and posteriorly to the cavernous sinus. As a consequence, *cavernous sinus thrombophlebitis* may occur as a complication of a sinus or orbital infection (see Chapter 91).

Epidemiology

Preseptal cellulitis is much more common than orbital cellulitis. In a review of 315 pediatric patients (age 18 years or younger) with either infection treated in two adjacent Boston hospitals between 1980 and 1998, 94% were preseptal cellulitis cases.[48a] Both conditions occur most often in young children: 75% of patients in the Boston study were younger than 5 years. Children with orbital cellulitis tend to be slightly older than children with preseptal cellulitis. The average age of orbital cellulitis patients in the Boston study was 5 years versus 3 years for preseptal cellulitis patients. Frequently, the term *orbital cellulitis* is used in the literature imprecisely to include cases of subperiosteal and orbital abscess in addition to cellulitis. The distinction is important clinically because abscesses usually require surgical drainage. Orbital cellulitis is the most common orbital infection in some pediatric series and subperiosteal abscess in others, whereas orbital abscess is rare (6% of cases in one series).[49] Subperiosteal abscess comprised 72% of cases in a series of 101 children with orbital infections.[50]

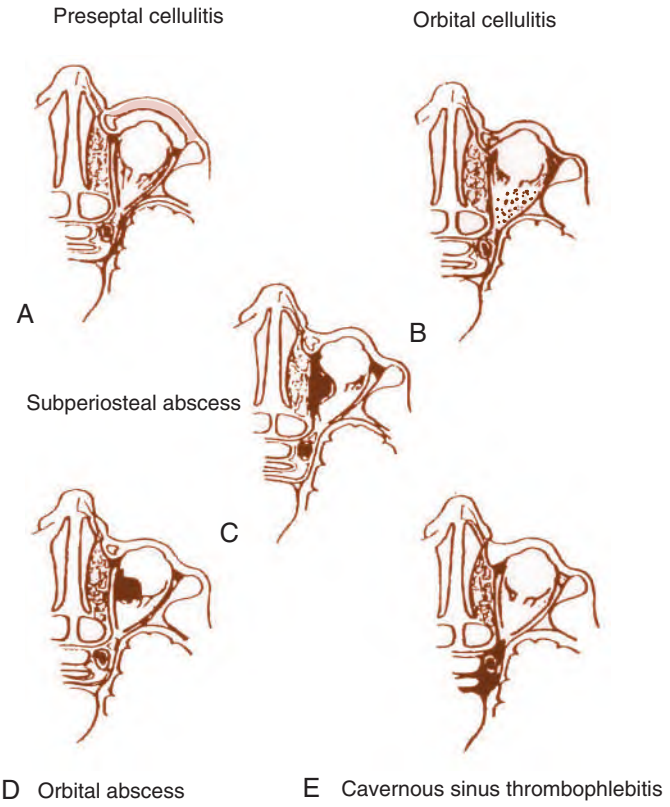

FIG. 116.8 Five diagrams illustrating preseptal cellulitis (A), orbital cellulitis (B), subperiosteal abscess (C), orbital abscess (D), and cavernous sinus thrombophlebitis (E). *(Modified from Chandler JR, Langenbrunner DJ, Stevens FR. The pathogenesis of orbital complications in acute sinusitis.* Laryngoscope. *1970;80:1414–1428.)*

Etiology and Bacteriology

Sinusitis causes up to 90% of all preseptal and orbital infections. Other causes of preseptal cellulitis include eyelid skin infections and (rarely) bacteremia. Other causes of orbital infections include dental infections, orbital trauma or surgery, and lacrimal system infections.

Preseptal cellulitis is usually caused by sinusitis. Cultures of the sinuses in these cases usually reveal the usual acute sinusitis pathogens, including *S. pneumoniae* and *H. influenzae*, although *S. aureus* may also play a role. Two other causes of preseptal cellulitis include bacterial superinfection of a rash or break in the eyelid skin and bacteremic seeding. The first may follow trauma, an insect bite, or herpetic lid lesions (herpes simplex or zoster). The pathogens are usually *S. aureus* or group A streptococci. Preseptal cellulitis that is part of a facial cellulitis or erysipelas is included in this category. Rare cases of group A streptococcal preseptal cellulitis have been complicated by either streptococcal toxic shock syndrome or eyelid necrosis.[51,52] *Pseudomonas aeruginosa* also caused lid necrosis as a complication of blepharitis and preseptal cellulitis in one case.[53] Other unusual causes of preseptal cellulitis include ringworm,[54] atypical mycobacteria,[55] and anthrax.[56] The second cause,

bacteremic seeding of the lids, occurs in infants and young children (usually younger than 3 years). This syndrome has become much less common since the introduction of *H. influenzae* type b (Hib) vaccine in 1990. Before the Hib vaccine, preseptal cellulitis was associated with bacteremia in 10% to 33% of cases, with 80% to 100% of these cases due to *H. influenzae*.[57–59] Studies in the Hib vaccine era have found that bacteremia is a very rare cause of preseptal cellulitis; a study of 35 such patients found none had positive blood cultures.[50] Streptococci, especially *S. pneumoniae* and group A streptococci, are the main causes of bacteremia now,[60] although nontypeable *H. influenzae* is still an occasional pathogen.[61]

Subperiosteal abscess is caused by ethmoid sinusitis in nearly all cases. Abscess cultures show *S. pneumoniae, S. anginosus*, group A streptococci, *H. influenzae,* and *S. aureus* as the major pathogens. A study from Toronto reported that, of 18 cases of subperiosteal abscess with positive cultures from surgical drainage, *S. anginosus* (44%) and *H. influenzae* (22%) were the major pathogens.[50] A study of children with sinogenic orbital cellulitis or subperiosteal abscess evaluated the changing bacteriology since the widespread use of the 7-valent pneumococcal conjugate vaccine (PCV7) and found a marked decrease in infections due to *S. pneumoniae* or viridans streptococci but an increase in *S. aureus* infections, including MRSA.[62] Brook and Frazier[63] found that subperiosteal abscesses in adults were also polymicrobial, with a similar mixture of aerobes and anaerobes. These cultures agreed with maxillary sinus puncture cultures obtained from the same patients. A study of 94 children hospitalized in Toronto between 2004 and 2009 with orbital cellulitis (45% of cases), subperiosteal abscess (47%), or orbital abscess (8%) found that *S. anginosus (milleri)* was the most common pathogen (44% of culture-positive cases), followed by *S. aureus,* group A streptococci, *S. pneumoniae*, and *H. influenzae*.[64] Anaerobes, including *Fusobacterium* and *Eikenella,* were isolated in 14% of culture-positive cases. A study of 53 patients (two-thirds adults) with sinogenic orbital or subperiosteal abscess found that the major pathogens were streptococci (37%), *S. aureus* (28%), gram-negative bacilli (17%), and anaerobes (19%).[65] MRSA accounted for 6.5% of cases; one-third of cultures grew more than one pathogen.

Orbital cellulitis and orbital abscess are usually caused by sinusitis, but rare cases occur after penetrating trauma, orbital surgery, canalicular surgery, peribulbar anesthesia for eye surgery, endophthalmitis, dental abscess, dacryocystitis, or dacryoadenitis.[66–70] These nonsinusitis etiologies may be more common in adults than children. In a study from Australia, 91% of children with orbital cellulitis or abscess had sinusitis, whereas only half of adults did.[71] The remaining adults had dacryocystitis, trauma, endophthalmitis, and secondarily infected nasal tumor as etiologies. There was no case of posterior extension of preseptal cellulitis in either children or adults in this study, and such cases are very rare.

An unusual cause of preseptal or orbital cellulitis is pneumococcal bacteremia. Cellulitis of the head and neck region from bacteremic pneumococcal infection is well described in patients with lupus erythematosus or hematologic disorders.[72,73] Patients with lupus who develop this may just have started corticosteroid therapy. Pneumococcal orbital cellulitis has also been described in a previously healthy adult without bacteremia.[74] *Pseudomonas* preseptal or orbital cellulitis may occur in neutropenic cancer patients secondary to *Pseudomonas* bacteremia.[75,76] Community-acquired MRSA is an important cause of orbital cellulitis in neonates and is associated with bacteremia.[77,78]

Clinical Manifestations

Preseptal and Orbital Cellulitis

Preseptal cellulitis must be distinguished from orbital cellulitis, a much more dangerous infection. The term *periorbital cellulitis,* sometimes used for preseptal cellulitis, should be avoided because it does not make this distinction clear. In preseptal and orbital cellulitis the lids are red and swollen. The lids may be swollen shut, but it is essential to examine the eye to evaluate visual acuity and extraocular movement. In preseptal cellulitis, vision is normal, there is no afferent pupillary defect, extraocular movements are full and painless, and there is no proptosis. In contrast, patients with orbital cellulitis have some degree of ophthalmoplegia or proptosis, or both. There is often deep eye pain and pain with eye movement. Proptosis may not be grossly apparent and should be measured (e.g., with the Hertel exophthalmometer); a difference of 2 mm or more is significant. Vision may be decreased, and an early warning sign may be an afferent pupillary defect. Fever and leukocytosis, usually present in children with preseptal or orbital cellulitis, may be absent in adults. Fever was present in 70% of pediatric cases but only 30% of adult cases in one series.[71]

Orbital and Subperiosteal Abscesses

Patients with an orbital or subperiosteal abscess usually present with marked lid swelling and erythema, eye pain, proptosis, marked ophthalmoplegia, and often vision loss. Most have fever. Because the abscess is medial or superomedial in nearly all cases, the eye is typically fixed looking "down and out" (Fig. 116.9).

Orbital Apex, Superior Orbital Fissure, and Cavernous Sinus Syndromes

Orbital apex syndrome is characterized by marked ophthalmoplegia and vision loss. The cranial nerves of the orbital apex are involved, which include the optic nerve and cranial nerves III, IV, VI, and the first division of V. There is often an afferent pupillary defect due to involvement of the optic nerve and hypoesthesia of the forehead due to involvement of the first division of cranial nerve V. Etiologies include vascular (e.g., carotid cavernous fistula), inflammatory (e.g., giant cell arteritis, Wegener's disease), neoplastic (e.g., lymphoma, head and neck cancers, neural tumors), and infectious.[79] In infectious orbital apex syndrome, unlike orbital cellulitis, marked vision loss and ophthalmoplegia may occur with minimal or no lid swelling or erythema. Overt signs of orbital inflammation may worsen subsequently. This syndrome is usually caused by infection in the adjacent posterior ethmoid or sphenoid sinuses, and most cases are due to invasive mold infections. Orbital apex syndrome is a well-known presentation of mucormycosis.[80] *Aspergillus* may cause an orbital apex syndrome in immunocompromised or normal hosts and may have a subacute presentation.[81,82] *Pseudallescheria boydii* has been described as an etiology in rare cases of invasive fungal infection involving the orbital apex.[83] Rare cases of orbital apex syndrome are due to bacteria.[84] Visual loss is usually irreversible.

If the infection is localized immediately anterior to the orbital apex, a "superior orbital fissure syndrome" may occur. This syndrome has the same cranial neuropathies as orbital apex syndrome except there is no involvement of the optic nerve. If the infection is posterior to the orbital apex, a "cavernous sinus syndrome" may occur. This has the same cranial neuropathies as orbital apex syndrome except with the added involvement of the second division of cranial nerve V and sometimes the oculosympathetic fibers. In addition, because the cavernous sinus is a venous plexus that extends to the opposite side, bilateral cranial neuropathies are typical. The superior orbital fissure, orbital apex, and cavernous sinus are contiguous, and the etiologies are similar.[79] Infections rarely respect the precise anatomic locations these syndromes imply, and infections may be in the cavernous sinus, for example, without having all the features of the cavernous sinus syndrome. Infectious etiologies for all of these syndromes include fungi, bacteria such as *S. aureus,* streptococci including *S. anginosus (milleri),* gram-negative bacilli, syphilis, and herpes zoster. Herpes zoster ophthalmicus (HZO) rarely may be complicated by complete unilateral ophthalmoplegia or

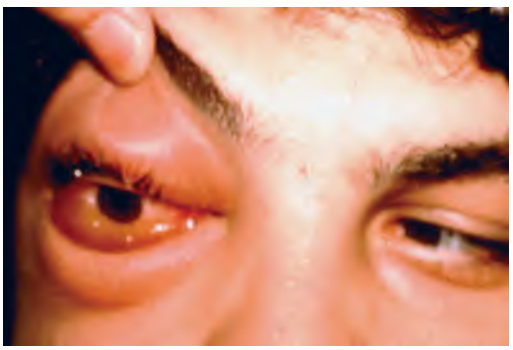

FIG. 116.9 **Patient with orbital abscess (eye looks "down and out").**

orbital apex syndrome. In a review of 20 cases, HZO preceded ophthalmoplegia in 75% and occurred concurrently in 20%.[85]

Cavernous Sinus Thrombophlebitis

Septic cavernous sinus thrombophlebitis is rare and should be suspected in any patient with orbital cellulitis who develops contralateral signs of orbital inflammation (lid swelling, proptosis, ophthalmoplegia) (see also Chapter 91). Spread to the opposite eye occurs through the cavernous sinus and usually occurs within 24 to 48 hours of the initial unilateral orbital findings.[86] Patients may also present with bilateral findings, including lid edema, chemosis, proptosis, ptosis, and ophthalmoplegia, or they may present with signs of bilateral neuropathies of some or all of cranial nerves III, IV, and VI but without the lid edema and erythema that typifies orbital cellulitis. The latter is especially true in cases of cavernous sinus thrombophlebitis that arise from skin infections of the middle third of the face or in dental infections, rather than primary orbital infections. In cavernous sinus thrombophlebitis there may be decreased sensation over the forehead and sometimes cheek due to involvement of the first or second division of cranial nerve V. Trigeminal nerve involvement may be seen in a quarter of patients with cavernous sinus thrombophlebitis but is not a feature of usual bacterial orbital cellulitis.[87] Early cases may present with unilateral findings of orbital cellulitis and cavernous sinus syndrome but with persistent headache and lethargy. This was illustrated in a case report of a child with cavernous sinus thrombophlebitis, sphenoid sinusitis, and *S. anginosus (milleri)* bacteremia in whom the clues to more serious infection were unrelenting headache, fever, and lethargy.[88] Visual loss may occur from venous congestion and ischemia. Patients are usually febrile and may be lethargic or obtunded. There is often sphenoid and posterior ethmoid sinusitis. *S. aureus* is the major pathogen, and cases of MRSA have also been described.[89] Other pathogens include streptococci, especially *S. anginosus (milleri)* group; anaerobes; and gram-negative bacilli.[90–92] Two cases with a subacute presentation involved *Actinomyces* in one and *Aggregatibacter actinomycetemcomitans* in the other.[93,94] In both cases, patients initially were misdiagnosed as having Tolosa-Hunt syndrome, an idiopathic, steroid-responsive inflammatory process involving the cavernous sinus.

Laboratory and Radiologic Studies

Laboratory studies (white blood cell count, blood cultures) should be obtained in all patients with preseptal or orbital cellulitis. Leukocytosis with a left shift is present in most patients. Blood cultures are rarely positive in older children and adults but may be positive in up to 8% of young children, as noted earlier.

The most helpful study in evaluating a patient with orbital infection is computed tomography (CT). A CT scan should be performed in any patient with orbital signs (ophthalmoplegia, proptosis, decreased vision, or a combination of these) because it is essential to identify an abscess that may require urgent drainage. Repeat scans should also be obtained in any patient with presumed uncomplicated orbital cellulitis who fails to improve or worsens on intravenous (IV) antibiotics alone. A CT scan may not be necessary in many cases of preseptal cellulitis because the diagnosis may be made clinically. However, several reports highlight the fact that in children orbital signs may be absent, yet they may have an orbital or subperiosteal abscess. Some authors advocate CT for all children with preseptal cellulitis, however, and report occasional cases of subperiosteal abscess that presented similar to preseptal cellulitis, with no proptosis, visual decrease, or ophthalmoplegia.[95] A retrospective study that included 111 children (median age, 7) with orbital or subperiosteal abscess on CT found that proptosis, ophthalmoplegia, and pain with eye movement were risk factors for abscess, but half lacked these findings.[96] This study found that marked lid inflammation with edema extending beyond the lid margins, high white blood count (neutrophil count > 10,000), and previous antibiotic therapy were also risk factors for abscess.

If performed, CT in preseptal cellulitis shows lid edema but no proptosis or inflammation ("streaking") of the orbital fat. Findings in orbital cellulitis usually include proptosis, streaking of the intraconal fat, and edema of the medial rectus muscle. In subperiosteal or orbital abscess there is a low-density mass effect with or without enhancement.[97] An air-fluid level within the mass is even more specific for abscess.[98] Lateral displacement of the medial rectus and displacement of the periosteum away from the lamina papyracea are findings that suggest subperiosteal abscess (Fig. 116.10). CT results alone lead to misdiagnoses, however, and cannot always be relied on to determine the need for surgery. In one study, CT missed the diagnosis for 2 of 10 subperiosteal abscesses and 1 of 5 orbital abscesses.[97] Another review of 159 patients with orbital complications of sinusitis described 4 patients who developed blindness from orbital abscess.[99] The abscess was not diagnosed by CT in any of these 4 patients before surgery.

If orbital apex syndrome is suspected, magnetic resonance imaging (MRI) or high-resolution CT with slice thickness of 3 mm or less, or both, should be obtained.[100] If cavernous sinus thrombosis is suspected, MRI with venography (MRV) should be performed. Findings in cavernous sinus thrombosis include flattening or bowing of the lateral wall of the cavernous sinus (best viewed on coronal images) and filling defects within the contrast-enhancing cavernous sinus.[86] Dilation of the superior ophthalmic vein due to venous obstruction is an indirect sign of cavernous sinus thrombosis. Contrast-enhanced thin-section CT also has a very high sensitivity for detecting cavernous sinus thrombophlebitis, and CT is the usual initial study performed in patients who present with orbital infections. Radiologists correctly diagnosed seven of eight cases of cavernous sinus thrombophlebitis in one retrospective study in which the images were viewed without any clinical information.[101] The differential diagnosis of bacterial orbital cellulitis includes orbital pseudotumor, tumor, and invasive fungal disease (invasive sinus aspergillosis and mucormycosis). Orbital pseudotumor is an idiopathic disease, more common in adults than children, that often manifests with painful ophthalmoplegia. It may appear with inflammatory proptosis, mimicking orbital cellulitis.[102] Patients with tumors of the orbit may present with acute inflammation mimicking orbital cellulitis. This has been described in primary ophthalmic rhabdomyosarcoma and retinoblastoma.[103,104] Rhinocerebral mucormycosis, which frequently manifests as an orbital cellulitis, is discussed in Chapter 258. Mucormycosis should be considered in any patient who presents with orbital cellulitis and who has risk factors for mucormycosis (e.g., poorly controlled diabetes mellitus, hematologic malignancies, immunosuppression, deferoxamine therapy). In contrast with typical bacterial orbital cellulitis, patients with rhinocerebral mucormycosis may have minimal lid erythema, more pain in the forehead or temple than in the eye, and early onset of decreased sensation in the first and second divisions of cranial nerve V. Invasive sinus aspergillosis usually invades from the sphenoid sinus and may manifest as a subacute orbital apex syndrome.

Therapy

Preseptal cellulitis due to sinusitis should be treated with antibiotics active against *S. aureus, S. pneumoniae,* and *H. influenzae*. Blood cultures should be obtained in very young children and in any patient with a fever or other signs of systemic illness. Initial antibiotics should be

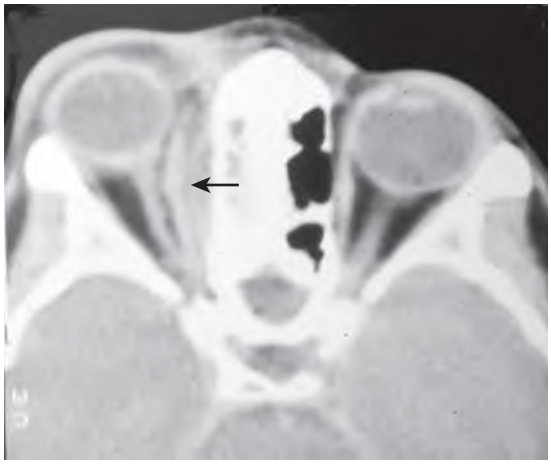

FIG. 116.10 Computed tomography scan of subperiosteal abscess (*arrow* points to abscess).

given intravenously in these cases. In older children and adults with mild preseptal cellulitis due to sinusitis, initial antibiotics may be oral (e.g., amoxicillin-clavulanate). In cases of preseptal cellulitis due to a skin lesion (e.g., superinfected abrasion or insect bite), oral antibiotics may be given if the infection is mild and there is no sign of systemic illness. Antibiotics that have activity against MRSA, in addition to streptococci and methicillin-susceptible *S. aureus*, should be chosen (e.g., trimethoprim-sulfamethoxazole plus amoxicillin). In countries (e.g., the Netherlands) or communities that have a very low incidence of MRSA, inclusion of an anti-MRSA antibiotic may not be necessary.

All patients with orbital infections (cellulitis, subperiosteal or orbital abscess) should be promptly treated with IV antibiotics and monitored closely for signs of visual compromise. Blood cultures should be drawn in all cases and sinus cultures obtained in patients with sinusitis. Nasal screening cultures for MRSA colonization may be helpful. Initial antibiotics should be broad spectrum with coverage against *S. aureus,* including MRSA; streptococci, including *S. pneumoniae*; *H. influenzae* and other gram-negative bacilli; and anaerobes. A regimen such as IV vancomycin, metronidazole, and ceftriaxone would provide this coverage and also provide adequate antibiotic levels in the central nervous system (CNS) in cases in which posterior spread of infection is a concern. In patients who are highly penicillin-allergic or intolerant of third-generation cephalosporins, levofloxacin or ciprofloxacin could be substituted for ceftriaxone. If there is no concern for CNS spread, IV vancomycin plus ampicillin-sulbactam (or piperacillin-tazobactam) would be a reasonable initial regimen. If *Pseudomonas* is a consideration (e.g., patients who are immunocompromised, have known sinus colonization with *Pseudomonas,* or who have received multiple antibiotics in recent months), then an antipseudomonal agent should be included. Antibiotics should be tailored based on culture results (e.g., blood, sinus, abscess drainage). Older children and adults with subperiosteal abscess usually require prompt surgical drainage in addition to broad-spectrum IV antibiotics, but young children with small, medial subperiosteal abscesses may respond to IV antibiotics alone. A study of 68 children with subperiosteal abscesses reported that two-thirds responded to medical therapy alone, whereas one-third required surgery.[105] The children who required surgery were older (8.3 vs. 6.2 years) and had larger abscesses on CT scan (>10 mm). Children with subperiosteal abscesses who are initially managed medically must be followed very closely, and any worsening should prompt surgical drainage of the abscess. Patients with orbital abscesses nearly always require immediate surgical drainage, in addition to broad-spectrum empirical therapy. Broad-spectrum combination antibiotic therapy (e.g., vancomycin, metronidazole, and a third- or fourth-generation cephalosporin) should also be used as initial therapy for acute bacterial cavernous sinus thrombosis secondary to orbital cellulitis. Because this infection carries a high risk of intracranial complications (e.g., brain abscess, subdural empyema), any regimen should include antibiotics that cross the blood-brain barrier. Surgical drainage of the primary focus of infection (e.g., sinusitis or dental abscess) should be performed, and patients should be monitored closely for any intracranial extension that may require surgical drainage.[106] The use of anticoagulation has been controversial[107] and is discussed further in Chapter 91.

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The complete reference list is available online at Expert Consult.

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N Hepatitis

117 Viral Hepatitis

Jules L. Dienstag

SHORT VIEW SUMMARY

ACUTE HEPATITIS

- Acute clinical illnesses caused by the five hepatitis viruses (hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], hepatitis D virus [HDV], and hepatitis E virus [HEV]) are similar.
- Illness ranges from asymptomatic to fulminant.
- Asymptomatic infections are 10 to 30 times more common than symptomatic ones.

CHRONIC HEPATITIS

- Chronic hepatitis affects more than 400 million people worldwide.
- HBV, HCV, and HDV cause chronic hepatitis.
- HEV causes protracted and chronic hepatitis only in immunosuppressed patients.

INDIVIDUAL HEPATITIS VIRUSES (SEE TABLE 117.1)

Hepatitis A Virus

- HAV is an RNA virus that is a member of the *Hepatovirus* genus.
- HAV is transmitted via the fecal-oral route.
- It typically causes an acute, self-limited illness, more often symptomatic in adults than in children.
- HAV is more severe in patients with preexisting chronic hepatitis B or C.
- Relapsing and cholestatic hepatitis may occur.
- Diagnosis is by serology (immunoglobulin M [IgM] anti-HAV) (see Table 117.2).
- Treatment beyond supportive care is usually not necessary.
- For prevention, highly effective HAV vaccines are available; these have markedly reduced incidence where used.
- Passive immunization with immune globulin intramuscularly is effective in postexposure prophylaxis.

Hepatitis B Virus

Virology and Epidemiology

- HBV is a double-stranded DNA virus in the *Orthohepadnavirus* genus and the Hepadnaviridae family; 10 genotypes have been identified.
- Worldwide, 250 million people are infected chronically with HBV.
- One million deaths annually result from complications of chronic infection—cirrhosis, hepatocellular carcinoma (HCC).
- Prevalence in Asia is estimated at greater than 10%, resulting primarily from perinatal transmission, after which the likelihood of acquiring chronic infection is 90%.
- In adults, transmission of hepatitis B occurs primarily as a result of high-risk behaviors (injection drug use, sexual activity) or after occupational exposure but resolves in more than 95% of otherwise healthy persons.

Diagnosis

- Acute hepatitis B is a symptomatic infection typified by right upper quadrant pain, nausea, malaise, jaundice, elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and IgM antibody to hepatitis B core antigen.
- Different categories of chronic infection are diagnosed on the basis of serologic testing and HBV DNA level (see Table 117.5).
- Liver biopsy is not required for diagnosis but may inform treatment decisions in chronic infection.

Treatment

- Indications are as follows (see Table 117.7):
  - Hepatitis B e antigen (HBeAg)–positive or HBeAg-negative patients with ALT greater than two times the upper limit of normal or moderate-to-severe hepatitis on liver biopsy and HBV DNA >20,000 IU/mL
  - HBeAg-negative patients with low-level HBV DNA but evidence of fibrosis or moderate-to-severe hepatitis on liver biopsy
  - Cirrhosis associated with chronic HBV irrespective of HBV DNA level
  - Inactive carrier (hepatitis B surface antigen [HBsAg] positive) preemptively when starting chemotherapy or other immunosuppressive therapy (including anti–tumor necrosis factor)
- Therapy is as follows (see Table 117.8):
  - Tenofovir disoproxil fumarate (TDF) as administered at 300 mg daily, or entecavir 0.5 mg daily (1-mg dose approved for prior lamivudine resistance but not a viable alternative to adding tenofovir); in patients with reduced creatinine clearance (estimated glomerular filtration rate [eGFR] <60 mL/min) or evidence of proximal tubular injury or osteoporosis, and according to some authorities all patients >60 years old, tenofovir alafenamide 25 mg daily is used instead of TDF.
  - Administration of 48 weeks of pegylated interferon (PEG IFN) in noncirrhotic HBeAg-positive patients is also an option.
  - Consider stopping oral therapy in HBeAg-positive patients 6 to 12 months after HBeAg seroconversion (HBeAg negative and anti-HBe positive); there is a ≥40% chance of HBeAg seroconversion after 5 years of therapy.
  - Indefinite treatment is used in patients with chronic HBeAg-negative hepatitis B; consider stopping therapy for HBsAg seroconversion.

Prevention

- Universal vaccination of infants begins at birth (three or more intramuscular doses).
- Prenatal maternal HBsAg screening is performed. If mother is HBsAg positive, hepatitis B immune globulin 0.5 mL is given at birth along with vaccination.
- Tenofovir 300 mg is administered starting in the third trimester in women with HBV DNA >2× 10^5 IU/mL.

Hepatitis D Virus

- HDV is a percutaneously transmitted, circular RNA virus (genus: *Deltavirus*) that requires HBV (or other hepadnaviruses) to replicate and persist.
- Acute coinfection can occur and follows the clinical course of acute HBV infection.
- HDV superinfection results in chronic infection in patients with prior chronic hepatitis B and has clinical features similar to those of chronic hepatitis B infection, although with increased severity and risk of progression to cirrhosis.
- The diagnosis is made by means of serologic testing for antibodies to HDV or by polymerase chain reaction (PCR) for HDV RNA.
- Oral antivirals for hepatitis B are not active against HDV, but prolonged treatment with PEG IFN may benefit a proportion of patients.

SHORT VIEW SUMMARY—cont'd

Hepatitis C Virus

Virology and Epidemiology

- HCV is a single-stranded RNA virus (genus: *Hepacivirus*) with six main genotypes (1–6); it exists as quasispecies because of its high mutation rate.
- HCV requires host lipid membrane assembly and secretion apparatus for replication.
- Worldwide, 71 million patients have chronic HCV infection, with more than 3 million residing in the United States.
- Transmission occurs predominantly through injection drug use, but other modes include blood transfusion before the availability of screening or nonsterile practices in which blood or body fluids are exchanged. (Note: The risk of hepatitis C is not increased in people with tattoos or in health workers.)
- Chronic HCV infection develops in at least 85% of patients with acute infection and, in the absence of treatment, results in cirrhosis in approximately 20% of patients after 20 years of infection.
- The annual incidence of HCC in persons with HCV-associated cirrhosis is 1% to 4%.
- Hepatitis C is the leading indication for liver transplantation in the United States.

Diagnosis

- Symptomatic hepatitis and jaundice develop in fewer than 10% to 20% of patients with acute hepatitis C, which often portends viral clearance.
- Chronic hepatitis C tends to be asymptomatic, although patients often complain of fatigue.
- Patients with HCV-associated cirrhosis may present clinically with complications of end-stage liver disease such as variceal bleeding, hepatic encephalopathy, or ascites.
- The detection of antibody to HCV is the initial diagnostic test, but PCR testing for HCV RNA distinguishes ongoing chronic infection (commonly) from prior exposure with subsequent clearance (rare).

Treatment

- The goal of therapy in chronic hepatitis C is to achieve a sustained virologic response (SVR), which is defined as undetectable HCV RNA 24 weeks after completion of therapy (12 weeks has been adopted as the SVR end point in contemporary clinical trials).
- The availability of direct-acting antivirals (DAAs), which are highly potent, well tolerated, and can be administered orally, has resulted in dramatic advances in treatment of hepatitis C. The September 2017 guidelines for treatment of hepatitis C from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America are presented as standard of care as follows:
  - Standard of care first-line agents for DAA-naïve patients, September 2017, are summarized in Table 117.9.
    - Genotype 1
      - Sofosbuvir-ledipasvir for 12 weeks (no cirrhosis or compensated cirrhosis; if no cirrhosis, not black, and HCV RNA $<6\times 10^6$ IU/mL, treatment duration 8 weeks)
      - Glecaprevir-pibrentasvir for 8 weeks (no cirrhosis) or 12 weeks (compensated cirrhosis)
      - Grazoprevir-elbasvir for 12 weeks (not recommended for genotype 1a if baseline elbasvir NS5A resistance present)
      - Sofosbuvir-velpatasvir for 12 weeks
    - Genotype 2
      - Glecaprevir-pibrentasvir for 8 weeks (no cirrhosis) or 12 weeks (compensated cirrhosis)
      - Sofosbuvir-velpatasvir for 12 weeks
    - Genotype 3
      - Glecaprevir-pibrentasvir for 8 weeks (no cirrhosis) or 12 weeks (compensated cirrhosis) (not recommended for PEG IFN–ribavirin–experienced patients)
      - Sofosbuvir-velpatasvir for 12 weeks (not recommended for PEG IFN–ribavirin–experienced patients; for baseline Y93H resistance-associated substitutions, add ribavirin or consider sofosbuvir-velpatasvir-voxilaprevir)
      - Additional regimens in compensated cirrhosis
        - Grazoprevr-elbasvir plus sofosbuvir for 12 weeks (not recommended for PEG IFN–ribavirin-naïve patients)
        - Sofosbuvir-velaprevir-voxilaprevir for 12 weeks (not recommended for PEG IFN–ribavirin-naïve patients)
    - Genotype 4
      - Glecaprevir-pibrentasvir for 8 weeks (no cirrhosis) or 12 weeks (compensated cirrhosis)
      - Sofosbuvir-velpatasvir for 12 weeks
      - Sofosbuvir-ledipasvir for 12 weeks (not recommended for PEG IFN–ribavirin–experienced patients with compensated cirrhosis)
      - Grazoprevr-elbasvir for 12 weeks (for PEG IFN–ribavirin–experienced, only for relapsers)
    - Genotype 5 or 6
      - Glecaprevir-pibrentasvir for 8 weeks (no cirrhosis) or 12 weeks (compensated cirrhosis)
      - Sofosbuvir-ledipasvir for 12 weeks
      - Sofosbuvir-velpatasvir for 12 weeks

Hepatitis E

- HEV is an RNA virus (genus: *Hepevirus*).
- It spreads through fecally contaminated water in endemic areas.
- HEV causes acute, self-limited hepatitis, similar to HAV, in normal hosts.
- Case-fatality rates are 0.9% to 2.8% in men and 20% in pregnant women, particularly in the third trimester.
- In immunosuppressed patients, particularly solid-organ transplant recipients, HEV can cause protracted infection, chronic hepatitis, and cirrhosis.
- Diagnosis is by serologic tests (IgM antibody to HEV) or PCR in blood or stool.
- With regard to treatment, acute hepatitis E is usually self-limited; chronic hepatitis E responds to ribavirin (preliminary data suggest responsiveness to sofosbuvir) therapy.
- Highly effective vaccines consisting of recombinant capsid proteins have been developed for use in endemic areas. One (Hecolin) is licensed in China.

Viral hepatitis is an infection that predominantly affects the liver but may also have systemic clinical manifestations. It is estimated that as many as 400 million persons have chronic viral hepatitis,[1] which, therefore, is the most common cause of chronic liver disease. Although the exact burden of acute viral hepatitis is not known, at least 1.4 million cases of hepatitis A occur worldwide annually. Thus, viral hepatitis is a major public health problem. The vast majority of cases of hepatitis are caused by one of five hepatotropic viruses: hepatitis A virus (HAV); hepatitis B virus (HBV); hepatitis C virus (HCV); hepatitis D (delta) virus (HDV); and hepatitis E virus (HEV). HBV, HCV, and HDV also cause chronic hepatitis, whereas HAV does not. HEV causes acute hepatitis in normal hosts but can cause protracted and chronic hepatitis in immunosuppressed patients (Table 117.1). Approximately 15% to 17% of cases of hepatitis have features similar to hepatitis caused by known viruses but remain unexplained and are therefore areas of search for occult viral agents. Putative viral agents for such cases, primarily in transfusion-associated hepatitis, have been described (hepatitis G, hepatitis GB, transfusion-transmitted virus, SEN virus),[2–4] but these do not appear to be human pathogens. Liver involvement may also be seen on occasion as part of systemic infections with herpes simplex virus, Epstein-Barr virus (EBV), varicella-zoster virus, enteroviruses, adenoviruses, yellow fever virus, mumps, rubella, and rubeola, but these viruses do not cause infections that primarily affect the liver.

The acute clinical illnesses caused by the five hepatitis viruses (A–E) range from asymptomatic to fulminant and fatal. The chronic infections caused by HBV, HCV, and HDV range from subclinical persistent infections to rapidly progressive chronic liver disease with cirrhosis and increased risk for hepatocellular carcinoma (HCC). HEV can also cause protracted and chronic infections in immunosuppressed patients (see later).

TABLE 117.1 Hepatitis Viruses and Characteristics of Infection

CHARACTERISTIC	A	B	C	D	E
Virus family	Picornaviridae	Hepadnaviridae	Flaviviridae	Unassigned	Hepeviridae
Genus	*Hepatovirus*	*Orthohepadnavirus*	*Hepacivirus*	*Deltavirus*	*Hepevirus*
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Incubation period (days)	15–48 (mean 30)	30–180 (mean 60–90)	15–160 (mean 50)	30–180 (mean 60–90)	14–60 (mean 40)
Mode of transmission					
Fecal-oral	Yes	No	No	No	Yes
Sexual	Possible	Yes	Rare	Yes	No
Blood	Rare	Yes	Yes	Yes	No[a]
Chronic infection	No	Yes	Yes	Yes	Yes[b]
Cirrhosis and hepatocellular carcinoma	No	Yes	Yes	With hepatitis B	No[c]

[a]Can be bloodborne in endemic areas.
[b]Acute hepatitis in normal hosts, protracted and chronic infection only in immunosuppressed patients.
[c]Cirrhosis can occur after chronic infection, which is confined to immunosuppressed patients.

Discussion of viral hepatitis in this chapter is divided into the following two sections: "Acute Viral Hepatitis" and "Chronic Viral Hepatitis."

ACUTE VIRAL HEPATITIS

Clinical Manifestations

The clinical manifestations of acute viral hepatitis are similar among the five hepatitis viruses, and no clinical features distinguish unequivocally one from the others, although certain epidemiologic patterns of transmission may suggest a particular virus.

Asymptomatic infections with the hepatitis viruses are approximately 10 to 30 times more common than symptomatic ones. These are most often recognized by rises in liver biochemical test results along with serologic markers of viral infections in patients being evaluated for nonspecific constitutional complaints (see later). The incubation periods of hepatitis vary with the individual virus (see later), and prodromal symptoms are common but quite varied in the individual patient. Approximately 25% of patients report the onset of symptoms as a "flulike" illness. Symptoms include malaise, fatigue, myalgia, arthralgia, and headache. Anorexia, nausea, and vomiting may occur, sometimes associated with alterations in olfaction and taste. Pharyngitis, coryza, and cough may also be present. Low-grade fever is common and more frequent in hepatitis A and E, rather than in hepatitis B or C, except when hepatitis B is associated with a serum sickness–like syndrome, in which a fever of 39.5°C to 40°C may be present. Dark urine and clay-colored stools may appear, usually 1 to 5 days before the onset of icterus, although a substantial portion of patients never become jaundiced. With the onset of jaundice, the constitutional symptoms generally abate but may continue during the entire icteric period. Right upper quadrant tenderness and discomfort are present as the liver enlarges, and in some patients a cholestatic clinical picture may develop, suggesting extrahepatic biliary obstruction. Splenomegaly and cervical lymphadenopathy are seen in 10% to 20% of patients.

As patients recover, constitutional symptoms resolve, but usually some liver enlargement persists, as do elevations of liver biochemical tests (see later). The duration of the posticteric phase is variable and ranges from 2 to 12 weeks. It is usually more prolonged in hepatitis B and C. Complete resolution of clinical and laboratory abnormalities is to be expected 1 to 2 months after the onset of jaundice in acute hepatitis A and 3 to 4 months after the onset of jaundice in 75% of cases of uncomplicated acute hepatitis B or C. In hepatitis E, acute cases are similar to those in hepatitis A, but protracted infection may occur in hepatitis E in immunosuppressed patients, and severe and fatal infection can occur in pregnant women (see later).

Laboratory Features

Serum aspartate aminotransferase (AST) and the alanine aminotransferase (ALT) activities increase to variable levels during the prodromal phase of acute hepatitis and precede elevations in bilirubin. The magnitude of AST and ALT elevations do not correlate closely with the extent of liver damage. Peak levels vary from 400 to 4000 international units (IU)/L, and maximums are usually reached when the patient becomes icteric. Jaundice, when present, reaches levels of 5 to 20 mg/dL and is usually equally divided between conjugated and unconjugated fractions. Neutropenia and lymphopenia may be present initially, followed by lymphocytosis with atypical lymphocytes. Prothrombin times should be followed because a prolonged value may indicate a severe hepatic synthetic defect, severe hepatocellular necrosis, and a poor prognosis. A diffuse but modest elevation of the serum globulin fraction is often present, and antibodies to smooth muscle and to other cell constituents can be seen.

Prognosis of Acute Hepatitis

The prognosis of patients with hepatitis A is excellent; nearly all previously healthy patients recover fully and without sequelae. Similarly, 95% to 99% of otherwise healthy, immunocompetent patients with acute hepatitis B recover completely. Hepatitis C is even less severe than hepatitis B during the acute phase, and fatalities are rare, although the precise case-fatality rate is unknown; chronic hepatitis C follows acute infection in approximately 85% of cases. Patients with simultaneous acute hepatitis B and acute hepatitis D do not necessarily have a more severe disease than those with acute hepatitis B alone, and the duration of hepatitis B infection will determine the chronicity of hepatitis. In contrast, hepatitis D superinfection of established chronic hepatitis B infection often leads to clinical deterioration (see later). Waterborne acute infection with HEV has a mortality rate of 0.6% to 2.8%[5] in men and up to 20%[6,7] in pregnant women. HEV can also cause chronic and severe hepatitis in immunosuppressed patients.[8]

Certain clinical and laboratory findings may be associated with more complicated and protracted courses of acute viral hepatitis. These include advanced age and serious underlying medical conditions. Presenting clinical features such as ascites, peripheral edema, and hepatic encephalopathy indicate a poorer prognosis. A prolonged prothrombin time, low serum albumin, hypoglycemia, and very high serum bilirubin indicate more severe hepatocellular damage. Patients with those clinical and laboratory findings should be hospitalized promptly.

Fulminant Hepatitis

Fulminant hepatitis is defined as severe liver failure developing within 8 weeks of the onset of symptoms and is the most feared complication of acute hepatitis. It is seen primarily with hepatitis B and D but may occur rarely in hepatitis A infection in older patients and in patients who also have chronic hepatitis B or C infection.[9] Hepatitis B infection of patients with underlying chronic hepatitis C may also lead to fulminant hepatic failure. Fulminant hepatitis is hardly ever seen in patients with hepatitis C alone. As noted earlier, hepatitis E may lead to acute liver failure uncommonly in men and in up to 20% of pregnant women.[5–7]

Considerable geographic variations exist in the causes of acute liver failure. Hepatitis E is the leading cause in India, and hepatitis B is the leading cause in France and Japan. Patients with acute fulminant

hepatitis usually present with hepatic encephalopathy, which may evolve into a deep coma. Liver size is reduced, bilirubin rises, and prothrombin time is markedly prolonged, even as aminotransferase levels drop. Ascites and peripheral edema are present, consistent with hepatic failure. Cerebral edema is common, and brainstem compression may occur. Also seen are gastrointestinal bleeding, sepsis, and respiratory failure. Cardiovascular collapse and renal failure are terminal events. The mortality rate is high (>80% in patients with deep coma), but those who survive have a complete clinical and laboratory recovery. Liver transplantation, if it can be performed in time, may be lifesaving in such patients. Drug-induced (acetaminophen) toxicity is the leading cause of hepatic failure in the United Kingdom and the United States.[10] Viral hepatitis was identified in only 12% of cases of fulminant hepatitis in the United States; HBV and HAV accounted for 7% and 4% of cases, respectively.[11,12]

Complications of Acute Hepatitis

Uncommonly, hepatitis A can be associated with relapsing hepatitis, occurring weeks to months after apparent recovery from hepatitis A.[13] Also uncommonly, a clinical picture of protracted cholestatic hepatitis may be present in patients with hepatitis A and persist for up to a year. Even with these complications, however, hepatitis A remains self-limited and does not progress to chronic liver disease.

A variety of immune-mediated complications may be associated with hepatitis B and C. During the prodromal phase of hepatitis B, a serum sickness–like syndrome may develop, characterized by arthritis or arthralgias, rash, angioedema, and, rarely, hematuria and proteinuria. Essential mixed cryoglobulinemia (EMC) and associated lymphoproliferative disorders can complicate chronic (not acute) hepatitis C, and hepatitis C may be associated with abnormalities in lipoprotein and glucose metabolism. The risk of chronic infection after acute hepatitis B in otherwise healthy adults is appropriately 1%, whereas the corresponding risk of chronicity after acute hepatitis C is 85% to 90%. Both chronic hepatitis B and C are associated with an increased risk of HCC. Chronic hepatitis B and C are discussed in the subsequent section of this chapter and in Chapters 145 and 154.

Agents of Viral Hepatitis

The characteristics of individual viruses that cause hepatitis are reviewed in Table 117.1. Additional details regarding epidemiology, virology, and pathogenesis are presented in chapters devoted to the individual pathogens.

Hepatitis A Virus (Also See Chapter 174)

HAV is a nonenveloped positive-strand virus that is 27 to 28 nm in diameter and is a member of the *Hepatovirus* genus in the Picornaviridae family. Human HAV strains are divided into four genotypes but appear to be of only one serotype. HAV is relatively stable under a variety of environmental conditions but can be inactivated by commonly used disinfecting chemicals, including hypochlorite and bleach (see Chapter 174). Person-to-person transmission by the fecal-oral route is the primary means of HAV transmission throughout the world.[14] Before the introduction of HAV vaccine, children were the major source of person-to-person transmission. Although foodborne and waterborne transmission are increasingly uncommon in the developed world, sporadic foodborne outbreaks continue to be reported, often linked to food products imported from developing countries. In 2017, a surge of new acute hepatitis A infections occurred via person-to-person spread, concentrated among homeless persons, persons using injection drugs, and their close personal contacts.

HAV replicates in the liver and is excreted in high concentrations in the stool and bile. The incubation period of illness is 15 to 45 days (mean of 30 days), and infectivity of virus in stool is present from 21 days before to 8 days after onset of jaundice. The highest concentration of virus in stool is in the 2-week period before jaundice develops (Fig. 117.1). Viremia begins during the prodrome and extends through the period of increased serum aminotransferase levels. Shedding of virus in stool may occur for a longer period in children than in adults. Although chronic shedding of HAV does not take place, virus shedding may recur during relapsing acute illness.

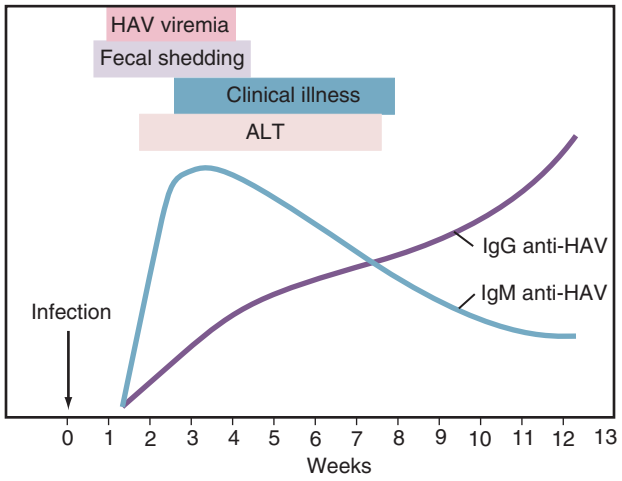

FIG. 117.1 Clinical, virologic, and serologic course of acute hepatitis A virus *(HAV)* infection. *ALT,* Alanine aminotransferase; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M.

Hepatitis A is typically an acute self-limited disease, but its clinical expression varies with age. The vast majority of infections are silent in children younger than 5 years, and rates of symptomatic infection and jaundice increase in older children and adults. Hepatitis A often begins with a mild prodrome; after 1 to 7 days dark urine and jaundice may appear. Two-thirds of patients recover by 2 months, 85% by 3 months, and nearly all by 6 months. Recovery is full and without sequelae, and chronic infection does not occur. Relapsing disease may occur after a typical initial course in 3% to 20% of patients. Occasionally, cholestatic hepatitis may complicate an acute course. HAV is a rare cause of fulminant hepatitis in the developed world but can cause severe hepatitis in individuals with preexisting hepatitis B or C and the elderly. During outbreaks of hepatitis A in homeless populations, mortality rates of approximately 3% to 4% have been reported.

Hepatitis B Virus (Also See Chapter 145)

HBV infects more than 250 million people worldwide.[15] It is the leading cause of chronic hepatitis, cirrhosis, and HCC. The sequelae of chronic infection account for more than 1 million deaths annually.

A partially double-stranded DNA virus in the Hepadnaviridae family, HBV replicates through reverse transcription from an RNA intermediate. The complete viral particle is 42 nm in diameter, outnumbered by abundant 22-nm spherical and filamentous subviral particles. HBV is divided into 10 genotypes (A–J) and multiple subgenotypes. The primary hosts for HBV are humans, but the envelope protein, hepatitis B surface antigen (HBsAg), has been detected in nonhuman primates. The primary cell for HBV replication is the hepatocyte, although a robust in vitro culture system has not been established. HBV does not appear to be directly cytopathic to the hepatocyte, and liver injury appears to be mediated by virus-specific cellular and humoral immune responses (see Chapter 145).

HBV is transmitted by cutaneous and mucosal exposure to infectious blood or bodily fluids, such as semen, saliva, cervical secretions, and tears, and can survive up to 7 days on environmental surfaces. The typical mode of transmission of HBV varies in part with the prevalence of infection. Perinatal transmission is the predominant mode in high-prevalence areas, whereas horizontal transmission, particularly in early childhood, accounts for most cases in intermediate-prevalence areas. Unprotected sexual intercourse and intravenous drug use are the major routes of spread in low-prevalence areas.

The sequence of virologic markers of acute, self-limited HBV infection is depicted in Fig. 117.2. The incubation period of hepatitis B is 30 to 180 days (mean, 60–90 days). The first marker is HBsAg within 1 to 12 weeks, usually in 8 to 12 weeks. HBsAg is ordinarily detected 2 to 6 weeks before ALT or AST elevations and clinical symptoms and remains detectable during the entire course of HBV infection. In typical acute

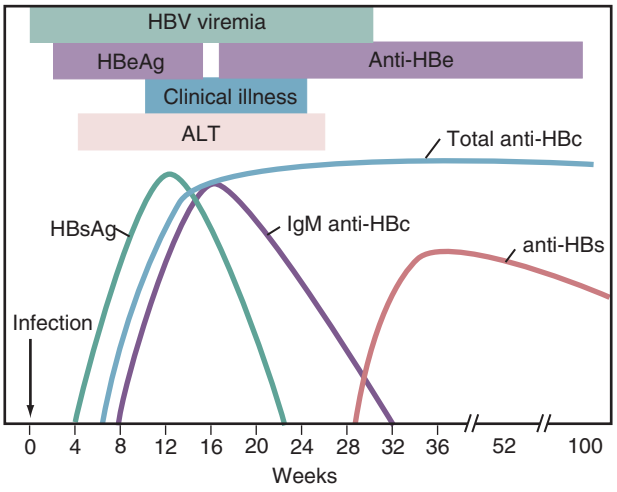

FIG. 117.2 Clinical, virologic, and serologic course of acute hepatitis B virus *(HBV)* infection. *ALT,* Alanine aminotransferase; *HBc,* hepatitis B core; *HBe,* hepatitis B envelope; *HBeAg,* hepatitis B e antigen; *HBs,* hepatitis B surface; *HBsAg,* hepatitis B surface antigen; IgM, immunoglobulin M.

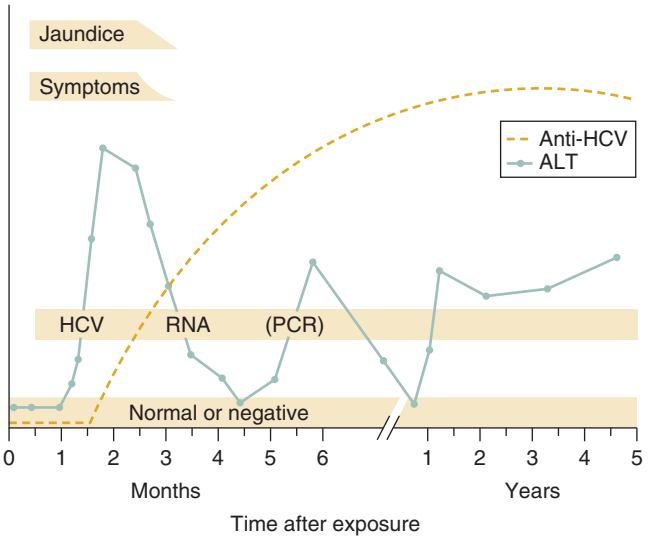

FIG. 117.3 Typical clinical, virologic, and serologic course of chronic hepatitis C virus *(HCV).* ALT, Alanine aminotransferase; PCR, polymerase chain reaction; RNA, ribonucleic acid. *(From Hoofnagle JH. Chronic hepatitis. In: Goldman L, Ausiello D, eds.* Cecil Medicine. *23rd ed. Philadelphia: Saunders; 2008.)*

cases, HBsAg becomes undetectable by 1 to 2 months after jaundice and rarely persists beyond 6 months. After HBsAg clears, anti-HBs becomes detectable and persists indefinitely. Anti-HBc can be present weeks to months before detection of anti-HBs. Hepatitis B e antigen (HBeAg), which appears concurrently with or shortly after the appearance of HBsAg, is associated with high levels of HBV replication and tends to be replaced by antibody to HBeAg (anti-HBe) beyond approximately 3 months.

Hepatitis C Virus (Also See Chapter 154)

HCV is a positive-strand RNA virus in the genus *Hepacivirus* of the family Flaviviridae. HCV is roughly spherical and is 55 nm in diameter. There are at least six major genotypes or clades, and a minor seventh genotype has been identified. The genotypes are highly diverse, but the extent of serotypic variation among genotypes is not well understood. The high level of virion turnover coupled with the absence of proofreading by the NS5B polymerase results in generation of multiple variants ("quasispecies") in an infected person. The use of autonomously replicating viral replicons and the establishment of a complete cell culture system have enabled detailed studies of HCV replication and identification of specific viral functions as targets for antiviral chemotherapy (see "Chronic Viral Hepatitis" later).

After infection, HCV RNA can be detected within days of exposure. The incubation period of hepatitis C is from 15 to 160 days (mean, 50 days). Viremia peaks 8 to 12 weeks after infection and then plateaus or drops to lower levels and persists in 85% to 90% of individuals (Fig. 117.3); the risk of chronicity after acute HCV infection has been linked to non-C *IL28B* haplotypes.[16] The major consequence of persistent HCV infection is hepatic fibrosis, which may progress to life-threatening cirrhosis and increased risk of HCC. This generally occurs more than 20 years after infection but can develop more rapidly in persons older than 50 years or those with immunosuppression or human immunodeficiency virus (HIV) infection (see Chapter 154).[17]

HCV RNA can be detected in blood, saliva, tears, seminal fluid, ascitic fluid, and cerebrospinal fluid; however, HCV infection is most often transmitted through percutaneous exposure to blood. In economically developed countries, most new HCV infections are related to intravenous drug use. HCV may also be transmitted between sexual partners and perinatally, although these modes of transmission are inefficient and much less frequent than in HBV infections. In developed nations, antibody to HCV is prevalent in 1% to 2% of the population. The World Health Organization (WHO) estimated that more than 185 million persons worldwide were infected with HCV; however, modeling of global HCV RNA prevalence data in 2015 suggested that the current prevalence of viremic HCV infection is 1% of the global population, corresponding to 71 million infected persons.[18]

Hepatitis D Virus (Also See Chapter 146)

HDV is a 32-nm circular, single-stranded RNA virus (genus: *Deltavirus*) that requires the presence of HBV or another hepadnavirus for replication. Therefore, HDV either can infect the host at the same time as HBV or can superinfect a host that is already infected with HBV. HDV has a viral envelope derived from HBV and has a similar tropism for hepatocytes. An in vitro culture system, however, has not been established for its growth, and thus the mechanism for injury of hepatocytes with HDV remains unclear. HDV prevalence generally mirrors prevalence of HBV worldwide; eight genotypes have been identified, but genotype 1 is predominant. It is primarily transmitted via parenteral routes, although sexual and intrafamilial transmission can also occur.

Simultaneous infection (coinfection) of HBV and HDV generally manifests as an acute self-limited hepatitis with full recovery, and chronic infection is seen in 2% of patients, driven primarily by chronic HBV infection. More severe acute infection can be seen, and fulminant hepatitis can occur. In contrast, HDV superinfection of a person with chronic HBV infection usually results in a severe infection, followed by chronic hepatitis D infection in 90% of patients. Fulminant hepatitis may occur and is 10 times more common in superinfection with HDV than in coinfection with HDV and HBV. In patients with chronic HDV infection, HDV is the dominant virus because it suppresses HBV replication. Once chronic HDV is established, the course of hepatitis is accelerated, and cirrhosis occurs in 60% to 80% of patients. If HDV is present, the risk of HCC is higher than with HBV infection alone.

Hepatitis E Virus (Also See Chapter 178)

HEV is a single-stranded, nonenveloped RNA virus that is 27 to 34 nm in diameter. It is the single member of the genus *Hepevirus* in the family Hepeviridae. HEV has four genotypes in humans (and a fifth genotype not detected in humans) and up to 24 subtypes. HEV is primarily enterically transmitted. Genotypes 1 and 2 are spread by means of fecally contaminated water in endemic areas and may be spread through blood transfusion, particularly in endemic areas. Person-to-person transmission is uncommon but has been documented in households. Highest rates of seroprevalence are in Asia, Africa, the Middle East, and Central America. Sporadic cases occur in Western countries, and, surprisingly, a relatively high seroprevalence (21%) has been found in the United States, apparently related to infection with attenuated genotypes 3 and 4, which are of limited pathogenicity and which have been linked to animal-reservoir (predominantly swine) exposure.

The incubation period of illness is 14 to 60 days (mean, 40 days), and clinical illness appears to be similar to acute hepatitis from other

hepatotropic viruses, although perhaps more severe than that seen with HAV. Fulminant hepatitis can occur, with case-fatality rates of 0.9% to 2.8% in men and up to 20% in pregnant women, particularly in the third trimester.[5–7] The reason for the markedly increased mortality in pregnant women is unclear but may be related to increased virus replication observed in pregnancy.[19] HEV can be detected in stool for 1 week before the onset of illness and for up to 2 weeks afterward (Fig. 117.4). Hepatitis E viremia is generally short in duration, but on occasion it can last up to 4 months.

HEV is not a cause of chronic hepatitis, except in immunosuppressed patients. These include solid-organ recipients, HIV-infected patients, and patients receiving chemotherapy for hematologic malignancies. In such patients, chronic HEV infection and progressive clinical liver disease have been reported to develop.[8,20–22]

Diagnosis

Serologic tests are available to enable making the diagnosis of acute hepatitis A, B, C, D, and E. An algorithm for a diagnostic approach to a patient with acute hepatitis begins with four serologic tests for the most common causes of viral hepatitis in the United States: HBsAg, immunoglobulin M (IgM) antibody to HAV (anti-HAV), IgM anti-HBc, and anti-HCV. Table 117.2 shows the interpretation of the results of those tests. Detection of HBeAg may be useful as a marker for viral replication and for relative infectivity late in the course of illness. Sensitive and specific tests are available for HBV DNA (see Chapter 145) and HCV RNA (see Chapter 154), and these are particularly useful in assessing the effect of antiviral therapy (see "Chronic Viral Hepatitis" later). If hepatitis E is under consideration, a serologic test for IgM antibody to HEV (IgM anti-HEV) or polymerase chain reaction (PCR) assay for HEV RNA in blood or stool can be sought from the Centers for Disease Control and Prevention.

Liver biopsies are not indicated in patients with acute, self-limited hepatitis. In protracted cases or in patients with cholestatic disease, liver biopsy may be helpful in establishing the diagnosis or differentiating the patient's presentation from that associated with other causes of liver injury. Typical findings in acute viral hepatitis include lobular disarray, apoptosis of hepatocytes, mononuclear cell infiltrates in portal and periportal areas, and cholestasis. Liver biopsies are seldom indicated in cases of fulminant hepatitis, and percutaneous biopsies are often contraindicated because of coagulation defects or thrombocytopenia.

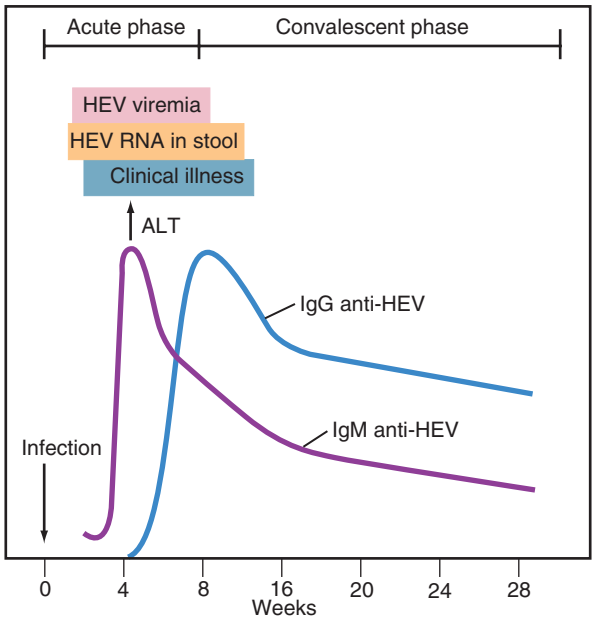

FIG. 117.4 Time course of clinical, virologic, and serologic events during acute hepatitis E virus *(HEV)* infection. *ALT,* Alanine aminotransferase; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M; *RNA,* ribonucleic acid.

Differential Diagnosis

A number of clinical entities can be considered in the differential diagnosis of acute hepatitis. These include drug-induced liver injury, ischemic hepatitis, autoimmune hepatitis, Budd-Chiari syndrome, Wilson disease, and syndromes related to pregnancy, such as acute fatty liver of pregnancy and the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP).

Other viruses may cause acute hepatitis on occasion. EBV is a relatively common cause, and 90% of patients with heterophile-positive mononucleosis have mild AST and ALT elevations, at two to five times normal (see Chapter 138). Cytomegalovirus (CMV) infection may also be associated with mild elevations of AST and ALT in otherwise healthy individuals but can be associated with more severe and systemic disease in immunosuppressed patients (see Chapter 137). Herpes simplex virus may cause a generalized infection that is associated with hepatic abnormalities, most commonly in neonates and immunocompromised children and adults.

Yellow fever may be associated with acute hepatitis and can be severe. Serum AST is usually higher than ALT, probably because of skeletal or myocardial injuries or both. In severe cases, aminotransferase levels may be greater than 2000 IU/L. Serum bilirubin is most often in the range of 5 to 10 mg/dL. Yellow fever should be suspected in a recent traveler to enzootic areas who did not receive adequate immunization. Acute hepatitis may also be seen in patients with leptospirosis[23] and Q fever.[24]

Treatment

Most cases of acute viral hepatitis do not require specific treatment, other than generally supportive and symptomatic measures. Other than for clinically severe cases, hospitalization is not required. Focused or

TABLE 117.2 Simplified Diagnostic Approach in Patients Presenting With Acute Hepatitis

	SEROLOGIC TESTS OF PATIENT'S SERUM			
DIAGNOSTIC INTERPRETATION	**HBsAg**	**IgM Anti-HAV**	**IgM Anti-HBc**	**Anti-HCV**
Acute hepatitis B	+	–	+	–
Chronic hepatitis B	+	–	–	–
Acute hepatitis A superimposed on chronic hepatitis B	+	+	–	–
Acute hepatitis A and B	+	+	+	–
Acute hepatitis A	–	+	–	–
Acute hepatitis A and B (HBsAg below detection threshold)	–	+	+	–
Acute hepatitis B (HBsAg below detection threshold)	–	–	+	–
Acute hepatitis C	–	–	–	+

HAV, Hepatitis A virus; *HBc,* hepatitis B core; *HBsAg,* hepatitis B surface antigen; *HCV,* hepatitis C virus; IgM, immunoglobulin M.
Modified from Longo D, Fauci A, Kasper D, et al. Harrison's Principles of Internal Medicine. *18th ed. New York: McGraw Hill; 2011.*

prolonged bed rest is also not necessary for full recovery, although patients may feel more comfortable with some restriction of physical activity. A high-caloric diet is desirable, but because many patients may experience nausea later in the day, the major caloric intake may be best tolerated early in the day. Intravenous feeding may be necessary if the patient cannot tolerate oral feeding. Glucocorticoid therapy has no proven value in acute viral hepatitis.

In acute hepatitis B, the prognosis is excellent and specific antiviral therapy is not necessary. In rare cases of severe acute hepatitis B, however, treatment with a nucleoside analogue at oral doses used for chronic hepatitis B is recommended by many consultants (see "Chronic Hepatitis B" later), even though its efficacy in acute hepatitis B has not been established in clinical trials.

Because progression to chronic infection is the rule after acute hepatitis C, treatment of acute cases of hepatitis C is recommended and is supported by a meta-analysis of data from clinical trials.[25] Still, because >20% (and up to 50% in some experiences) of acute hepatitis C cases resolve spontaneously, current recommendations are to observe for 6 months after onset of acute hepatitis C and to reserve treatment for those who do not recover spontaneously. Treatment consists of 8 to 12 weeks of therapy with one of the four current-generation, all-oral, highly effective direct-acting antiviral (DAA) agents used for chronic hepatitis C (see later discussion of treatment of chronic hepatitis C).[26] In the setting of an acute needlestick injury derived from a patient with known or suspected hepatitis C, the individual who was stuck should be monitored with HCV RNA and AST and ALT tests, and should receive treatment for acute hepatitis C infection as noted earlier.

As noted earlier, most acute cases of hepatitis E are also self-limited and do not require specific therapy; however, uncommonly, acute cases may be severe, and ribavirin (RBV) has been used effectively in individual cases with apparently good clinical responses and reduction of HEV RNA levels in blood.[27,28] Supporting the use of RBV in severe acute hepatitis E are observations of the effectiveness of RBV therapy in achieving a sustained virologic response (SVR) in organ-allograft recipients with chronic hepatitis E.[29] Hepatitis E can be a severe and fatal disease in pregnant women, and therapy is necessary in such cases; however, RBV is contraindicated in pregnancy because of its teratogenicity. Studies of its potential use in this setting are worthy of consideration.[30] Anecdotal effectiveness of sofosbuvir (SOF) in severe, persistent hepatitis E has been reported but not confirmed in cinical trials.

Prevention

Hepatitis A

Both passive and active immunoprophylaxis are available against hepatitis A (see Chapter 316). Immune globulin (IG) preparations used to contain sufficient anti-HAV concentrations to provide protection; however, as reported in 2017, the reduction in levels of anti-HAV in plasma donors has been reflected by reduced potencies of commercial IGs used for hepatitis A prophylaxis.[31] Therefore the US Public Health Service has updated IG doses for postexposure or preexposure prophylaxis. Instead of 0.02 mL/kg,[32] the recommended IG dose has been increased to 0.1 mL/kg (7 mL in a 70-kg adult) for preexposure prophylaxis in persons planning up to a month of travel to an endemic area and for postexposure prophylaxis (household, sexual, institutional). For travelers to endemic areas who plan up to 2 months of travel or longer, the IG dose is 0.2 mL/kg (to be repeated every 2 months for travel lasting longer than 2 months).[33] Administration is recommended as early as possible after exposure and is effective as late as 2 weeks after exposure. Prophylaxis is not necessary for those who have already received hepatitis A vaccine or for those known to have serum anti-HAV. For postexposure prophylaxis against HAV for individuals 12 months to 40 years of age, a single dose of hepatitis A vaccine is as effective[34] and is preferred to IG when practical for both preexposure and postexposure prophylaxis. For those younger than 12 months or older than 40, immunocompromised persons, and those with chronic liver disease, IG is recommended at the new doses described earlier.

Highly effective inactivated hepatitis A vaccines are available and have been part of the childhood immunization schedule since 2006 in the United States. Based on persistent levels of anti-HAV after vaccination, protection has been predicted to last at least 25 to 30 years.[35] The availability of this vaccine has resulted in a dramatic reduction of hepatitis A in all areas where vaccine use has been extensive (see Chapter 174). Patients with chronic hepatitis B or C have an increased risk of severe hepatitis when infected with HAV and should therefore also receive hepatitis A vaccine.

Hepatitis B

Vaccines against hepatitis B are now part of childhood immunization schedules in the United States and in most developed countries; the first dose should be administered within the first 24 hours of life. Hepatitis B vaccine is now recommended for individuals with frequent exposures to HBV infections, such as health care workers exposed to blood and household and sexual contacts of persons with chronic HBV infection. Included as recommended candidates for the vaccine are injection drug users, residents and staff of institutions for developmentally disabled persons, adults with chronic liver disease, adults with end-stage renal disease, adults with HIV infection, and diabetics younger than age 60.[36] HBV vaccines are recombinant preparations (Recombivax HB [Merck, Rahway, NJ] and Engerix-B [GlaxoSmithKline, Brentford, London]), which are available individually or as part of combinations with HAV vaccine (Twinrix [GlaxoSmithKline]) or with DPT (diphtheria, pertussis, tetanus) and inactivated polio vaccine for children (Pediarix [GlaxoSmithKline]) (see Chapter 316). A new recombinant hepatitis B vaccine with a novel adjuvant (CpG 1018, a CpG-containing oligonucleotide sequence that activates Toll-like 9 receptors), Heplisav-B [Dynavax, Berkeley, CA], was approved in 2017 for adults aged 18 or older; two intramuscular injections given a month apart were shown to induce protective antibody in a higher proportion than three intramuscular injections (at time 0, 1 month, and 6 months) with Engerix-B, especially among vaccine recipients with type 2 diabetes.

For postexposure prophylaxis after exposure to HBV, a combination of hepatitis B immune globulin (HBIG) (0.06 mL/kg) for rapid presence of antibody and hepatitis B vaccine (full course) for long-lasting immunity is recommended for those who have not been vaccinated. This is recommended for percutaneous inoculation or transmucosal exposure to HBV-containing bodily fluids and for sexual contact with an individual with hepatitis B (see Chapter 316). All pregnant women should be tested for circulating HBsAg, and HBIG (0.5 mL) should be given to infants as soon as possible after birth but within 12 hours of delivery in conjunction with a dose of hepatitis B vaccine. Additional doses of vaccine are indicated at 1 month and 6 months of age.

Hepatitis C

IG is not effective in prevention of hepatitis C. Development of vaccines to hepatitis C is impeded by the extensive viral heterogeneity of HCV. For persons with multiple sexual partners or sexually transmitted diseases, the likelihood of transmission of HCV is increased, and use of condoms is recommended. Persons with hepatitis C should avoid sharing razors, toothbrushes, and nail clippers with sexual partners and family members.

Hepatitis D

No product is available specifically to prevent transmission of HDV. The major approach to prevention of hepatitis D is prevention of hepatitis B through vaccination with HBV vaccines. Persons with chronic HBV infection should avoid percutaneous exposure and intimate contact with persons who have HDV infection.

Hepatitis E

IG, even produced from populations where hepatitis E is highly endemic, does not appear to provide protection against infection with HEV.[37]

A recombinant hepatitis E capsid protein vaccine (Hecolin [Xiamen Innovax Biotech, Xiamen, China]) was highly protective against infection with HEV (100% efficacy) in a large-scale trial and was licensed in China in 2011.[38] Another recombinant HEV capsid protein vaccine developed by GlaxoSmithKline in collaboration with the US Army has also been shown to be highly effective (95.5% protection against HEV infection after three doses)[39] but has not been approved by the US Food and Drug Administration (FDA) (see Chapter 178 for further details). Vaccines against HEV would be directed at areas of high prevalence for infection, as noted earlier.

CHRONIC VIRAL HEPATITIS

The term *chronic viral hepatitis* is used to describe protracted hepatocellular necrosis and inflammation, often with fibrosis, that lasts longer than 6 months and is caused by HBV, HCV, HBV-associated HDV, or HEV. Nonviral causes of chronic hepatitis that may be confused clinically with chronic viral hepatitis include autoimmune hepatitis; metabolic-genetic disorders (Wilson disease, hereditary hemochromatosis, α_1-antitrypsin deficiency); alcoholic liver disease; nonalcoholic fatty liver disease; drug-induced liver disease; and granulomatous disorders. The chronic viral hepatitides, however, are readily distinguished from these other forms of chronic hepatitis with serologic or virologic testing. Classified histologically by the degree of hepatocellular necrosis and inflammation (grade) and fibrosis (stage; Table 117.3),[40–42] chronic viral hepatitis may be mild (even sometimes without liver injury at all, representing an inactive carrier state), moderate, or severe. With the potential to culminate in cirrhosis, portal hypertension, and even HCC, chronic viral hepatitis ranks as the fifth most common cause of human deaths worldwide and the tenth most common cause of deaths in the United States. In the United States, chronic viral hepatitis has been estimated to result in annual economic losses that exceed $1 billion. Left to follow its natural history, chronic viral hepatitis could account for an even more substantial health and economic burden in coming generations; however, a vaccine to prevent hepatitis B and highly effective antiviral therapies for both hepatitis B and C have already been shown and will continue to reduce the morbidity and mortality of this human scourge.

Neither of the enteric RNA hepatitis viruses, hepatitis A and hepatitis E, causes chronic hepatitis; however, acute hepatitis A can be followed by a protracted, cholestatic syndrome that may last many months.[43] Hepatitis E can cause a protracted and chronic hepatitis in immunosuppressed patients (see later). Similarly, rare instances have been reported in which classic autoimmune hepatitis was preceded and presumably triggered by an episode of acute viral hepatitis A, B, or C.[44–46] Both CMV and EBV have been implicated as agents of acute hepatitis, primarily in patients with immunocompromise, but in immunocompetent patients with systemic acute CMV or EBV infection (e.g., infectious mononucleosis), transient elevations of serum aminotransferase and alkaline phosphatase activities are common. Neither agent is a likely contributor to chronic hepatitis.

In all forms of chronic viral hepatitis, liver injury does not result directly from a cytopathic effect of the virus but instead from an ongoing host-mediated cytolytic T-cell response to virus-infected hepatocytes that is ineffective in achieving adequate clearance of all virus-infected cells.

TABLE 117.3 Contemporary Histologic Classification of Chronic Hepatitis According to the Modified Histologic Activity Index (HAI) of Ishak and Colleagues and the METAVIR Scale

	HAI	METAVIR
Necroinflammatory Activity (Grade)		
Periportal necrosis, bridging necrosis	0–4	0–3, 0–1
Intralobular necrosis, confluent	0–6	
Intralobular necrosis, focal	0–4	0–2
Portal inflammation	0–4	0–3
TOTAL	0–18	A0–A3[a]
Fibrosis (Stage)		
None	0	F0
Portal (some)	1	F1
Portal (most)	2	F1
Bridging (few)	3	F2
Bridging (many)	4	F3
Incomplete cirrhosis	5	F4
Cirrhosis	6	F4
TOTAL	6	4

[a]Necroinflammatory activity: A0, none; A1, mild; A2, moderate; A3, severe.

Chronic Hepatitis B

In persons in whom HBV infection fails to clear during acute infection, chronic infection is characterized serologically by persistence in serum of the HBV envelope protein, HBsAg. Among cases of chronic hepatitis B, several important distinctions, based on levels of HBV replication, epidemiologic considerations, and viral variants, merit attention (Table 117.4).

Distinctions Based on Relative Levels of Hepatitis B Virus Replication

Among patients with chronic hepatitis B, a distinction can be drawn between those with highly replicative HBV infection (>10^5–10^6 IU/mL) and those with levels of replication below this threshold. In the relatively replicative phase of chronic hepatitis B, levels of HBV DNA are high (detectable in the past with insensitive hybridization assays or, currently, at levels that exceed 10^5 to 10^6 IU/mL with sensitive amplification assays such as PCR and transcription-mediated amplification [TMA]); transmissibility of infection to contacts is favored; HBeAg, another serologic marker of HBV replication, is detectable; the expression of HBV nucleocapsid antigens (primarily hepatitis B core antigen [HBcAg]) in hepatocytes is demonstrable; and clinical markers of liver injury are present. Such patients tend to have moderate-to-severe chronic hepatitis B.[47]

At an annual incidence of approximately 10% to 15%, persons with highly replicative chronic hepatitis B lose markers of high replication and undergo spontaneous conversion to a relatively low replicative state characterized by limited infectivity and liver injury and loss of HBeAg and of detectable hepatocyte expression of HBcAg.[48–51] Such patients tend to have clinically mild chronic hepatitis or are even inactive carriers of the virus. Unlike hepatitis C, in which any level of virus replication can be associated with liver injury, in chronic HBV infection a threshold exists, on the order of approximately 10^3 to 10^4 IU/mL, below which liver injury is negligible or absent.[52–54] The distinction in level of HBV replication between these two relative phases of chronic HBV infection is reflected by a dramatic difference in infectivity. Babies born to mothers with high-level HBV replication (HBeAg-reactive, HBV DNA ≥10^6 IU/mL) have a 90% chance of chronic HBV infection, compared with babies born to mothers with low-level HBV replication, whose likelihood of chronic HBV infection is 10% or less.[55] Similarly, a person who sustains a needlestick injury from a needle contaminated by blood from someone with highly replicative chronic HBV infection has a greater than 30% chance of infection, but the likelihood of infection is only 0.1% if the needlestick derives from a person with low-level HBV replication.[56] Similar distinctions occur between the two groups in sexual transmission. Inactive hepatitis B carriers, who have low-level viremia, absent or negligible histologic activity, normal liver biochemical test results, and minimal infectivity, can undergo HBsAg–to–anti-HBs

TABLE 117.4 Distinctions Among Patients With Chronic Hepatitis B

Distinction Based on Levels of HBV Replication
HBV DNA ≥10^5–10^6 IU/mL vs. ≤10^3–10^4 IU/mL Wild-type HBeAg reactive vs. HBeAg nonreactive
Distinctions Based on Epidemiologic Considerations
High-prevalence areas: perinatal acquisition, host tolerance, clinically inapparent acute infection, chronicity >90%, high risk of cirrhosis and HCC Low-prevalence areas: adolescent or adult sexual or percutaneous acquisition, host intolerance, clinically apparent acute hepatitis, chronicity <1%, low risk of cirrhosis and HCC
Distinction Based on Viral Variants
Wild-type, HBeAg-reactive vs. precore or core-promoter (HBeAg-negative) variants

HBeAg, Hepatitis B e antigen; *HBV,* hepatitis B virus; *HCC,* hepatocellular carcinoma; *IU,* international units.

seroconversion (i.e., the serologic hallmark of recovery from hepatitis B) but at a frequency of only 1% to 2% per year.[57,58] In the setting of immunologic compromise (e.g., cytotoxic chemotherapy, immunosuppression for organ transplantation, anti–tumor necrosis factor-α [TNF-α] therapy for inflammatory bowel disease or rheumatologic disorders, HIV infection), inactive carriers and even persons who have recovered from hepatitis B can have reactivation, potentially severe, of hepatitis B.[59–61] Among the complications of chronic hepatitis B is HCC, postulated to be associated with incorporation of HBV DNA (but not at a recognized uniform site) into the host genome.[62–64] Ironically, conversion from a state of free episomal HBV DNA to one in which HBV DNA is integrated into the host genome tends to occur, in nature, as HBV infection converts from highly replicative to minimally replicative. In all likelihood, integration of HBV DNA into host DNA does not rely on this change in replicative status; instead, both integration and reduced replication tend to occur after prolonged HBV infection. Areas of high HCC and HBV prevalence overlap geographically[63]; the relative risk of HCC among persons with HBsAg is 100-fold higher than in persons without this marker of HBV infection.[62] Observations have shown that among persons with HBsAg, the risk of HCC resides primarily among those with markers of high-level HBV replication.[65,66] Similarly, severity and progression of chronic hepatitis B are more pronounced in patients with high levels of HBV replication.[49,67,68] Thus the level of HBV replication has a profound influence over the clinical expression of chronic hepatitis B.

Distinctions Based on Epidemiologic Considerations

Chronic hepatitis B follows acute HBV infection in more than 90% of neonates born to mothers with chronic hepatitis B but in only approximately 1% of immunocompetent adults with clinically apparent acute hepatitis B.[69–71] In Asia and sub-Saharan Africa, the prevalence of HBV infection is high, exceeding 10% of the population, and in many Western countries, such as the United States, prevalence rates of less than 1% are the rule. These differences in frequency translate into marked distinctions in clinical expression of HBV infection.

In high-prevalence areas, women of childbearing age have the high likelihood of infection characteristic of the population at large; consequently, the risk of perinatal transmission of HBV infection from infected mother to her baby is high and represents the most common mode of HBV transmission in the population. Acquired in the perinatal period, HBV infection is unlikely to be accompanied by clinically apparent acute hepatitis but almost universally results in chronic infection, a reflection of what appears to be tolerance of the virus by the host immune system,[69] even though some immunologic responses to HBV have been demonstrated in newborns. Although most such infected persons can have mild asymptomatic chronic hepatitis B during childhood and early to middle adulthood, when high-level HBV replication tends to be accompanied by no more than minimal necroinflammatory liver injury, the lifetime risk of succumbing to chronic hepatitis B in such high-HBV-prevalence populations can reach 40%, the result of liver injury linked to high HBV replication in the middle decades and beyond, culminating in cirrhosis and HCC.[62]

In contrast, in low-prevalence areas (e.g., United States, western Europe), the limited frequency of HBV infection in the general population does not support a large cohort of infected women of childbearing age; therefore, the frequency of perinatal transmission is low. Instead, most HBV infections in such Western countries occur during adolescence and early adulthood, enhanced by behaviors (e.g., sexual activity, injection drug use, occupational exposure to blood and contaminated instruments) that foster the spread of bloodborne agents. Such infections result typically in a robust host-immune response to the presence of HBV on hepatocyte membranes, recognized clinically as acute hepatitis, and the cytolytic T-cell response is usually sufficient to eradicate HBV infection. Chronicity of hepatitis B under these circumstances is rare (≤1%),[70,72] and even among those with chronic hepatitis B in such low-prevalence HBV populations, progression to cirrhosis, and especially to HCC, is much less likely. Therefore, hepatitis B tends to be a chronic progressive disorder associated with a risk of HCC in high-prevalence populations but an acute self-limited illness with a low risk of HCC in low-prevalence populations.

What appears to drive the distinction between hepatitis B acquired in infancy and hepatitis B acquired in adulthood is the level of immunologic tolerance to HBV—high in the former group and low in the latter. In fact, most persons with chronic hepatitis B do not recall having had an acute hepatitis-like illness (i.e., an episode in which the host immune system mounted a vigorous attack on HBV-infected liver cells). In this vein, the clinical expression of HBV infection in the host with immunocompromise resembles the pattern that occurs in high-prevalence early-life acquisition areas (high likelihood of chronic infection and its consequences) rather than the pattern in low-prevalence adulthood-acquired infection. Some authorities distinguish between an immune-tolerant phase of chronic HBV infection during the early decades of life (high-level HBV replication with near-normal biochemical markers of inflammation, ALT activity, and liver injury) and an immune-clearance phase in later decades (with levels of liver injury more appropriate to the level of HBV replication). This categorization, of course, does not apply to patients who acquire HBV infection during adulthood and who are immunologically intolerant of the virus from the outset of infection. Even among those infected at birth (e.g., as is the rule in high-HBV-prevalence Asian countries), liver inflammatory activity and fibrosis occur even in early decades,[73] and many infected persons have protracted periods of inactive liver injury during the so-called immune-clearance period. Therefore, a more accurate distinction after perinatally acquired infection is between relatively high levels of immunologic tolerance (or a dissociation between HBV replication and necroinflammatory liver injury) during the early decades of life and substantially lower levels of tolerance (and a link between HBV replication and necroinflammatory liver injury) during later decades. Ultimately, over the lifetime of such patients, except during the early decades, the degree of progression of liver disease does correlate with the level of HBV replication.[65–68]

At least 10 genotypes of HBV have been identified, varying in geographic distribution, but understanding of the impact of genotype on the severity and consequences of chronic hepatitis B is evolving.[74] For example, genotype C is more likely than genotype B to result in progressive chronic hepatitis B and HCC and to be associated with later HBeAg seroconversion.[75–77] Generally, HBV genotype considerations tend to be clinically irrelevant in most settings.

Distinctions Based on Viral Variants

The distinction between high-replication HBeAg-reactive and low-replication HBeAg-negative chronic hepatitis B has been complicated by the recognition of a variant of chronic hepatitis B, HBeAg-negative chronic hepatitis B. In this subset of patients with chronic hepatitis B, HBeAg is undetectable, but other markers of enhanced HBV replication (HBV DNA, intrahepatocytic HBcAg), elevation of serum aminotransferase activity, and histologic evidence of chronic liver injury are present. With mutations in the precore region of the HBV genome (precore mutations or core-promoter mutations [see Chapter 145]), these patients have HBV infection in which the gene for the soluble nucleocapsid HBeAg protein cannot be transcribed or translated.[78–81]

In general, these mutations are acquired later in the natural history of chronic hepatitis B among persons infected early in life (i.e., they follow infection with wild-type HBV infection).[82] The exception to this observation is patients with precore-mutant fulminant hepatitis B in whom HBeAg-negative infection is transmitted perinatally or horizontally from persons with precore-mutant hepatitis B.[83,84] Still, all patients with these mutations have circulating serum anti-HBe instead of HBeAg. The most common precore mutation represents a G-to-A mutation at nucleotide 1896, which results in a stop codon in the precore gene, where initiation of HBeAg transcription occurs. In HBV genotype A, the nucleotide at position 1858 is C, adjacent, complementary, and strongly bound to nucleotide G at position 1896 in the loop structure of this part of the viral genome. Because the C_{1858}-G_{1896} bond is so strong, mutations have to occur at both of these sites for a precore mutation to occur, which is rare; therefore, precore mutations are seldom seen in patients with HBV genotype A. In contrast, in genotypes other than A, the nucleotide at position 1858 is T, adjacent, complementary, and unstably bound to nucleotide 1896 in the HBV genome loop structure. Because the bond between T_{1858} and G_{1896} is so unstable, G_{1896}A mutations can occur readily, without the need for a complementary mutation at position 1858. Therefore,

precore mutations occur primarily among persons with HBV genotypes other than A.[85] Consequently, precore mutations and HBeAg-negative chronic hepatitis tended to be relatively uncommon in parts of the world (e.g., the United States) in which genotype A predominates but are common in other parts of the world (e.g., Mediterranean countries, Europe, Asia) in which other genotypes are prevalent.[85,86] Although wild-type chronic hepatitis B predominates in the United States, almost all contemporary cases of chronic hepatitis B in Europe and the Mediterranean are HBeAg negative; in the United States, HBeAg-negative hepatitis B, once rare, now accounts for up to 40% of cases, fueled by migration from these other countries.[74,82]

Levels of HBV DNA tend to be lower in patients with HBeAg-negative chronic hepatitis B, but episodic flares in necroinflammatory activity are common, as are severe and progressive chronic hepatitis and its consequences, cirrhosis and HCC.[58] Important distinctions in response to antiviral therapy between wild-type HBeAg-reactive and mutant HBeAg-negative chronic hepatitis B are discussed subsequently.

Pathophysiology and Natural History

Like the other human hepatitis viruses, HBV is not cytopathic but instead engenders an endogenous cytolytic T-cell response to virus-infected hepatocytes.[87] Although nucleocapsid HBV antigens appear to be the target for cytolytic T cells, the complex cellular and humoral host factors, and the interaction among these factors, that determine the severity, duration, and outcome of hepatitis B are poorly understood. As noted, some authorities have postulated that periods of relative inactivity followed by periods of accelerated liver injury represent an immune-tolerance phase and an immune-intolerance or immune-clearance phase, respectively, in the natural history of chronic hepatitis B.[54] Such a model, however, is too simplistic and fails to account for demonstrated immune responses or for low-level or episodic liver injury that occurs during periods postulated to represent a tolerance phase, for periods of quiescence that can occur later in the natural history of chronic hepatitis B, for reactivations that can occur at any time during the course of chronic hepatitis B, or for waxing and waning necroinflammatory activity that occurs so commonly in HBeAg-negative chronic hepatitis B. Currently, the consensus view is that viral proteins are presented by antigen-presenting cells to $CD4^+$ (Th1) lymphocytes and to $CD8^+$ (Th2) lymphocytes. In acute, self-limited HBV infection, the $CD4^+$/Th1 response dominates, supporting cytolytic T-cell destruction of viral antigen-expressing hepatocytes. In chronic hepatitis B, Th2 responses dominate, and the weaker cytolytic T-cell response to HBV-infected hepatocytes is insufficient to clear virus-infected cells but sufficient to maintain inefficient but persistent hepatocyte injury. Evidence in experimental chimpanzee infection, however, suggests that this adaptive cellular immune response plays a secondary or "mop-up" role after the innate immune response, which clears 90% of the virus before, and without any, liver injury.[88–91] Evidence has been marshaled as well to support the presence of T-cell exhaustion in chronic hepatitis B. The pathogenesis and natural history of chronic hepatitis B are covered in more detail in Chapter 145.

Clinical Manifestations

In chronic hepatitis B, symptoms run the gamut from absent to severe, debilitating, and life-threatening.[67] Among inactive hepatitis B carriers and persons with mild-to-moderate chronic hepatitis B, symptoms are usually absent, although some with mild-to-moderate chronic hepatitis B report fatigue and, less commonly, right upper quadrant discomfort or "fullness." More severe and advanced cases can be associated with fatigue and jaundice, but persons with compensated cirrhosis may have no symptoms at all. Decompensated cirrhosis may be accompanied by fatigue, jaundice, loss of muscle mass (weight loss), ascites, edema, bruising (coagulopathy), gastrointestinal bleeding (gastroesophageal varices or portal hypertensive gastropathy), and hepatic encephalopathy. As is the case for acute hepatitis B and its associated serum-sickness-like prodromal syndrome, chronic hepatitis B may be complicated by immune-complex manifestations, including cutaneous vasculitis, arthritis, glomerulonephritis, and generalized vasculitis.[92]

Viral and laboratory markers of HBV infection are summarized in Table 117.5. The biochemical hallmark of chronic hepatitis B is elevation of serum aminotransferase activity, with normal to near-normal alkaline phosphatase activity. In severe, progressive, and decompensated chronic hepatitis B, bilirubin levels can increase (hepatic excretory dysfunction); albumin can fall, and prothrombin time can become prolonged (hepatic synthetic defect); and hypersplenism can occur (primarily thrombocytopenia and leukopenia). Autoantibodies are usually absent but may be present at low levels.

Histologic features of chronic viral hepatitis vary from absence of necrosis and inflammation to architectural distortion and fibrosis characteristic of cirrhosis. In general, histologic injury (grade) and fibrosis (stage) are categorized as mild, moderate, or severe. The level of necroinflammatory activity or injury is based on periportal necrosis, portal inflammation, and intralobular necrosis. Mild activity is confined to portal tracts, and necrosis and inflammation spilling beyond the limiting plate of periportal hepatocytes (interface hepatitis) signify a more severe injury with increased potential for progression. The degree of fibrosis is based on the localization and extent of scar tissue; fibrosis confined to portal areas is mild, and fibrosis that reaches beyond the portal tract (septal or bridging fibrosis), especially that which links portal tracts to other portal tracts or to central veins, connotes a more advanced and progressive process (see Table 117.3).[1,93]

Treatment

The goal of antiviral therapy in chronic hepatitis B is prevention of clinical and histologic progression, which, in turn, can be achieved with eradication or, more likely, suppression of HBV replication to below the threshold for liver injury (10^3–10^4 IU/mL).[53] In patients with HBeAg-reactive chronic hepatitis B, HBeAg to anti-HBe seroconversion tends to be associated (in up to approximately 80% of cases) with a sustained reduction in HBV replication that persists even after therapy is discontinued. Therefore, in HBeAg-reactive chronic hepatitis B, HBeAg seroconversion is a potential end point of therapy, after a consolidation period. For noncirrhotic HBeAg-positive patients, therapy should be continued for an additional 6 months after HBeAg seroconversion. Moreover, Lee and colleagues[94] found a higher rate of durable HBeAg seroconversion after extending treatment with lamivudine to 12 months, and most authorities would recommend a full 12-month consolidation period after HBeAg seroconversion in patients who had acquired HBV infection in infancy (as is common among Asian patients) and even potentially longer (or indefinitely) in cirrhotic patients.[94–97] In patients

TABLE 117.5 Viral and Laboratory Markers of Hepatitis B Virus Infection

DIAGNOSIS	HBsAg	Anti-HBs	IgM Anti-HBc	IgG Anti-HBc	HBeAg	Anti-HBe	ALT
Acute hepatitis	+	–	+	–	+	–	Elevated
Recovered (immune)	–	+	–	+	–	+	Normal
HBeAg-positive chronic hepatitis B	+	–	–	+	+	–	Elevated
HBeAg-negative chronic hepatitis B	+	–	–	+	–	+	Elevated (may be intermittent)
Vaccinated (immune)	–	+	–	–	–	–	Normal
Inactive carrier	+	–	–	+	–	+	Normal

ALT, Alanine aminotransferase; *HBc,* hepatitis B core (antigen); *HBe, HBeAg,* hepatitis B e antigen; *HBs, HBsAg,* hepatitis B surface antigen; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M.