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Endogenous *Candida* endophthalmitis

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Intraocular *Candida* infections, although uncommon, represent an important clinical problem owing to the potential for visual loss, which can be bilateral. *Candida* chorioretinitis and endophthalmitis are complications of systemic candidiasis with extension of the fungal pathogens to the uvea and retina. Early diagnosis and prompt management significantly affect the visual prognosis for these patients. This review evaluates the current literature on *Candida* endophthalmitis and includes discussion on presentation, diagnosis and management strategies. New systemic and intravitreal antifungal agents are also reviewed in the context of the management of intraocular fungal infection.

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Etiology & pathogenesis

Candida spp. form part of the human flora where they exist as commensals on the mucosal surface of the respiratory, gastrointestinal and female genital tracts. Disturbance of the body's immune system is generally required for these organisms to become pathogenic. *Candida* is the most common cause of nosocomial fungal infection and, although there is a recent trend towards an increase in the non-*albicans* spp., *Candida albicans* is still the most common organism isolated in candidemia [1–3]. In a large prospective study of more than 1000 patients with candidemia, Chen and colleagues reported that *C. albicans* was the most common species (50.4%), followed by *Candida tropicalis* (20.5%), *Candida parapsilosis* (14.2%) and *Candida glabrata* (12.0%). There were 0–2 isolates of *Candida krusei* per year [1].

The incidence of endogenous fungal endophthalmitis in patients with candidemia has been reported to range from 9 to 45% [4–9]. However, data from Feman and colleagues showed that, in patients with disseminated fungal disease, *Candida* chorioretinitis and endophthalmitis occurred in approximately 2.5% of their cases. This low figure may signify that the current trend for prophylaxis and prompt early treatment when *Candida* is

detected in blood cultures [10] has decreased the incidence of ocular complications dramatically [11]. In part, this may also be due to the superior ocular penetration of fluconazole (as compared with amphotericin B [AMB]), which is now used more frequently as antifungal prophylaxis in high-risk situations and also in the systemic treatment of candidal endophthalmitis.

Candida chorioretinitis and endophthalmitis occur predominantly as a result of candidemia seeding the eye, although cases occurring in otherwise healthy individuals have been very rarely reported [12]. While *C. albicans* is the most common form of fungal endogenous endophthalmitis [13], other *Candida* spp. may rarely cause this [14–16], with not much difference in the pattern of prevalent species noted in systemic candidemia. Uncommonly, *Candida* infection may occur after penetrating trauma or intraocular surgery and this type of intraocular inflammation is referred to as exogenous endophthalmitis.

Risk factors for the development of candidemia and endogenous fungal endophthalmitis are related mainly to suppression of the antifungal immune mechanisms or to procedures that increase the risk of blood-borne infection. Well-established factors include: immunosuppressive diseases, such as uncontrolled diabetes mellitus, cancer, therapy with

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broad-spectrum antibiotics and immunosuppressive drugs, major surgery, especially intra-abdominal surgery, intravenous hyperalimentation, indwelling intravenous catheters, and intravenous drug use [17–19], as well as neutropenia, which is the most common underlying condition associated with fungemia [20]. In a retrospective study involving 46 patients with fungal endophthalmitis, neutrophil counts equal to or less than 500 cells/ml were noted in approximately 70% of patients [19] and neutropenia was also shown to be associated with a poor response to antifungal treatment [21]. *C. albicans* endophthalmitis can also be seen in the postpartum period or after abortion, presumably as a complication of transient candidemia [22,23].

Despite the very high incidence of mucosal candidiasis, *Candida* retinitis is very uncommon in HIV-infected patients in the absence of other risk factors [24,25]. In a large retrospective series of 1163 HIV-infected patients, Jabs reported a single (<0.1%) case of *Candida* retinitis in a patient who was an intravenous drug user. He attributed this low incidence to the fact that immunity against systemic candidiasis is not dependent on cell-mediated immunity, in contrast to cytomegalovirus infection (e.g., retinitis) or cryptococcal infection. Instead it depends mainly on neutrophil cellular activity, which is not severely disturbed in HIV infection [24].

Newborns with low birth weight and prolonged hospital stay are at risk of developing candidemia. Although the occurrence of ocular infection is very unusual in this age group [26], close follow-up of newborns who survive candidemia is still essential as, rarely, preterm infants with successfully treated candidemia may develop a fungal abscess in the crystalline lens, as a result of sequestration of *Candida*. The organisms then escape the effect of systemic antifungal drugs [27]. In addition, *Candida* sepsis was found to be associated independently with progression of retinopathy of prematurity and the need for surgical intervention in extremely low-birth-weight neonates [28]. Fungal infections may cause release of proinflammatory cytokines that aggravate retinal neovascularization in retinopathy of prematurity [29].

In contrast to deep and disseminated fungal infection, the presence of superficial fungal infection is not itself a risk for developing ocular infection. Feman and colleagues found no cases of fungal endophthalmitis or chorioretinitis among the 32 patients with superficial fungal infection examined [11]. However, *Candida* endophthalmitis may develop in patients receiving antifungal therapy, as they may have a resistant organism [11].

Pathology

The choroid is the primary site of infection in the eye with secondary involvement of the retina (chorioretinitis) (FIGURE 1) and, from there, *Candida* spreads into the vitreous [17]. The inflammation is usually suppurative in nature with formation of multiple small vitreous abscesses [17], but a combination of granulomatous and suppurative inflammation has also been described [9]. Small foci of retinal damage are seen with *Candida* retinitis compared with extensive retinal necrosis with *Aspergillus* infection [17].

Presentation & clinical features

Patients with ocular *Candida* infection usually present with a subacute onset of floaters and blurred vision that may be associated with ocular discomfort and photophobia [11]. Early or peripheral fungal lesions may be asymptomatic, with patient's referral for ocular consultation being on the basis of a positive blood culture or diagnosis of systemic fungal infection. In a report that reviewed cases of culture-positive endogenous endophthalmitis, Binder and colleagues showed that, in cases with yeast infection, nearly half the patients did not have any detectable associated infectious focus beyond the blood, whereas the most common additional infectious focus among these patients was urinary tract infection, seen in 30% of cases [30].

Conjunctival injection and inflammation in the anterior chamber with or without a hypopyon may be present (FIGURE 2). Inflammatory cells may also be deposited at the back of the cornea (keratic precipitates). The hallmark for the diagnosis of *Candida* chorioretinitis is the presence of a fluffy creamy white lesion at the level of the retina and choroid that is usually associated with vitreous haze (FIGURE 3A) [4]. The lesions are commonly multiple and can be bilateral, hence the importance of examining both eyes even in patients with unioocular symptoms. Progression of an active lesion is noted by forward protrusion into the vitreous cavity, a sign first described by Villafont and colleagues in 1964 [31]. The inflammation may extend into the vitreous and sometimes intravitreal puff ball-like lesions are seen, which represent vitreous abscesses (FIGURE 3B).

Nonspecific lesions, such as intraretinal hemorrhages, nerve fiber layer infarcts and white centered hemorrhages (Roth spots) may be seen in the fundus in 10–20% of patients with candidemia. The presence of these lesions is not diagnostic and may be caused by either ocular candidiasis or associated systemic disease [4,32,33]. Serial ophthalmological examination is usually helpful to determine the nature of these lesions [33]. Retinal vascular occlusion may occur with fungal infection [19,34] and is usually associated with poor visual outcome [19].

Diagnosis

The diagnosis of *Candida* endophthalmitis is usually based on the appearance of the typical fundus lesion(s) in a patient with disseminated *Candida* infection or significant risk factors. In this context, isolation of the organism from urine, blood or other suspected sites such as intravenous lines and indwelling catheters supports the presumptive diagnosis. Positive *Candida* blood cultures occur in only 50–75% of patients with *Candida* endophthalmitis [33], presumably because some patients only have transient or intermittent fungemia. Martinez-Vazques and colleagues reported seven (47%) positive cultures in 15 cases of suspected *C. albicans* endophthalmitis complicating intravenous drug abuse [35]. The yield of positive cultures from vitreous samples is usually low in cases with fungal endophthalmitis. In a retrospective study by Tanaka and colleagues, positive cultures were found in only 38% of vitreous specimens in

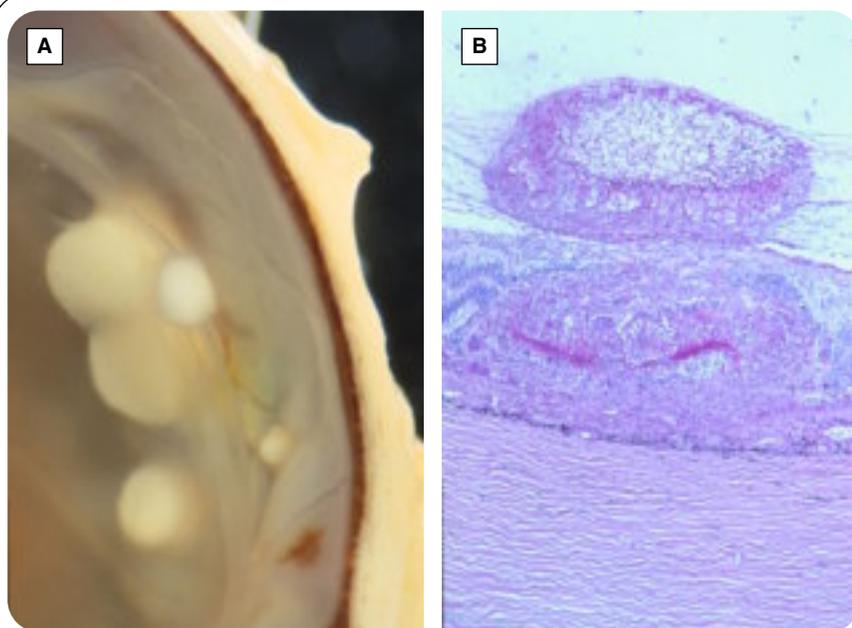


Figure 1. (A) Macrosection of an eye showing *Candida* abscesses. (B) Histopathological section showing an abscess in choroid invading the retina and with vitreous cells.

patients with endogenous fungal endophthalmitis. The authors attributed these results to several factors, including culture techniques and presurgical antimicrobial treatment [19].

Specimens for vitreous cultures obtained during vitrectomy surgery may be more sensitive in making the diagnosis than those obtained by vitreous needle biopsy. In a recent report that included 14 patients with fungal endophthalmitis, four cases who had a negative culture when the sample was taken via a needle tap were found to be positive when another biopsy was taken during vitrectomy [36]. This may in part be explained by fungal infection starting in the choroid and extending through the retina to the posterior part of the vitreous. Pathogens are thus present mainly in the opacified vitreous near the retina and can only be sampled during vitrectomy from posterior vitreous near the retina and not by vitreous tap that aspirates anterior and central vitreous [36].

Detection of *C. albicans* DNA in intraocular fluid can be carried out using PCR assay. This method has been shown to be sensitive and rapid and overcomes the limitations of vitreous fluid culture [37]. It also does not require viable organisms and can be performed on a small sample volume [38]. With routine cultures, the likelihood of obtaining positive culture results from the aqueous humor is much less than those from the vitreous [39,40], but PCR may be able to detect *Candida* DNA in aqueous samples taken through an anterior chamber paracentesis, which is an easier and less-invasive procedure when compared with vitreous aspiration or biopsy. Rapid detection of non-*albicans* spp. by PCR would permit the proper selection of antimicrobial treatment, as in species that are expected to be azole-resistant.

However, PCR may detect DNA from live or dead organisms and this should be remembered when interpreting results in patients already receiving treatment. Okhravi and associates

used combined PCR assay and restriction fragment length polymorphism analysis with different oligonucleotide primers to detect fungi in vitreous fluid and identify the specific *Candida* spp. causing the infection. Of four studied eyes, PCR products were found in three eyes and only those that tested positive with PCR responded to antifungal therapy, whereas the PCR-negative specimen was also negative by culture and did not respond to antifungal drugs [40].

Early detection

Published rates of endophthalmitis complicating candidemia vary widely and this is probably owing to differences in the patient population studied and prophylactic/systemic treatment regimens used. The consequences of unrecognized endophthalmitis are severe, which warrants formal ophthalmological assessment after detection of candidemia. An initial nega-

tive review should be followed by another at 2 weeks. In a prospective study of 31 patients with candidemia, the incidence of chorioretinitis was found to be 26% (eight patients), with 16% (five patients) diagnosed on their initial ocular consultation and three patients diagnosed within a 2-week period of their first review. The authors reported no evidence of ocular candidiasis in other patients who continued to be examined for up to 24 weeks [8]. As *Candida* endophthalmitis could be initially mistaken for noninfective uveitis [30,41], ophthalmologists need to maintain a high index of suspicion for patients with intraocular inflammation and a history of systemic immunosuppression, intravenous drug use or recent history of invasive surgical procedures [41]. Clinicians involved in the management of patients with candidemia should be aware of the potential for

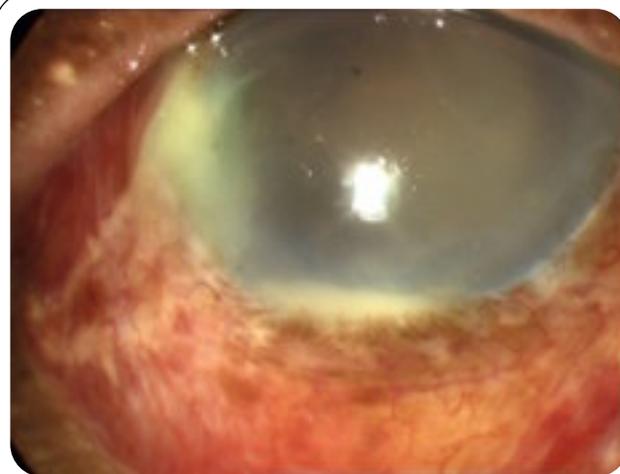


Figure 2. Hypopyon in an eye with intraocular *Candida* infection.

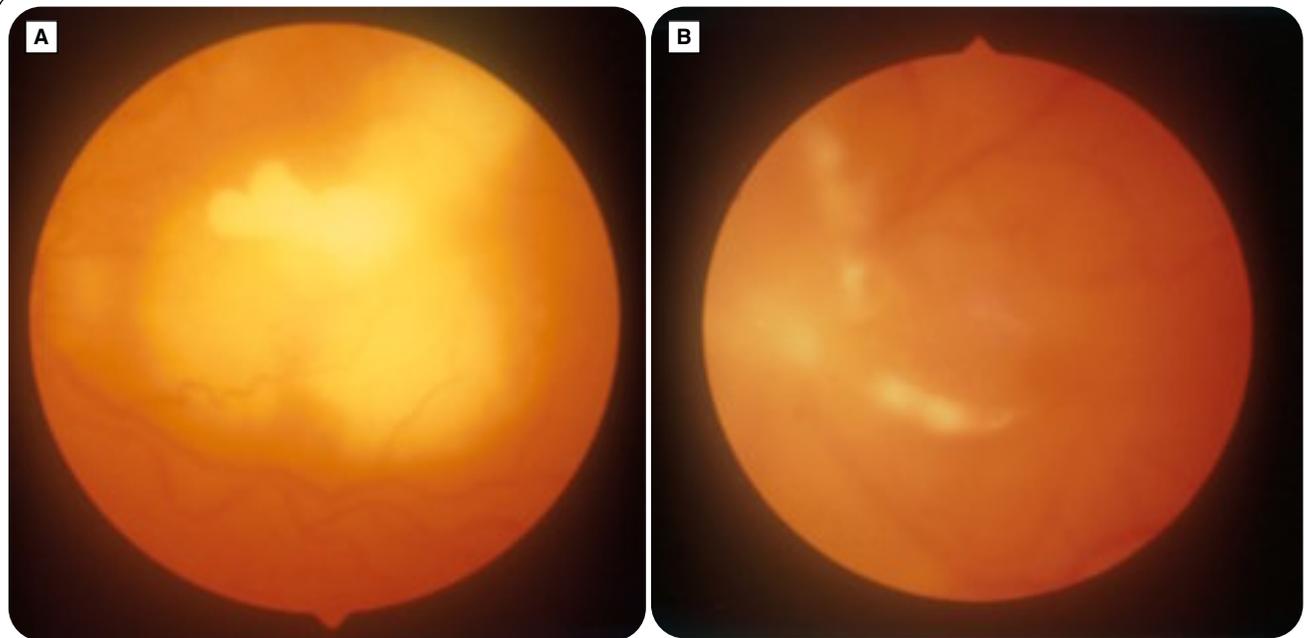


Figure 3. (A) Creamy white lesion classic of intraocular *Candida*. (B) Puff ball appearance of *Candida* infection extending into the vitreous.

eye involvement. Early consideration of ophthalmological evaluation should be given and is essential if the patient has visual symptoms or the eye is red.

Treatment

Patients with *Candida* chorioretinitis need to have the type and extent of their disease diagnosed, any complications detected and any underlying systemic cause or risk factor defined. Treatment should be instituted as soon as the diagnosis is made, in collaboration with the treating physician, with the aim to treat both the systemic and ocular candidiasis. Therapy should be continued until complete resolution of visible lesions. There are no randomized controlled trials on the duration of therapy for fungal eye disease. Clinical guidelines recommend courses of 6–12 weeks of therapy to ensure complete eradication of the systemic disease as well as any residual fungus in the eye [42].

Systemic antifungal therapy

Systemic antimycotic agents can be used to treat ocular candidiasis, as well as the systemic infection. However, once the fungus has penetrated the blood–eye barrier and crossed Bruch's membrane into the retina, the infection is then no longer confined to the choroid, so drugs that cross the blood–retinal barrier and achieve high intraocular levels must be used [43], usually in combination with intravitreal therapy when the vitreous is involved.

AMB is a polyene antibiotic that binds to the ergosterol of the fungal cell membrane forming an ergosterol–AMB complex. This complex forms pores in

the fungal cell membrane, resulting in increased cell membrane permeability and, ultimately, cell death [44]. The drug exhibits wide antifungal activity [45], although limited activity has been reported against some of the non-*C. albicans* spp. [46–49]. This drug is available commercially as AMB deoxycholate (D-AMB) since combining the drug with sodium deoxycholate, a bile salt carrier, increases its aqueous solubility. The drug is given as an intravenous infusion in dextrose over several hours in a dose of up to 1.5 mg/kg/day in severe cases, although a dosage above 1 mg/kg is often associated with high toxicity. When given parenterally, it is highly protein bound and distributes poorly to body fluids and tissues. Although the presence of intraocular inflammation enhances AMB penetration into the eye, systemically delivered AMB (even as lipid formulations) does not achieve therapeutic concentrations in the eye and is therefore not effective in the management of *Candida* retinitis extending into the vitreous [50,51]. The

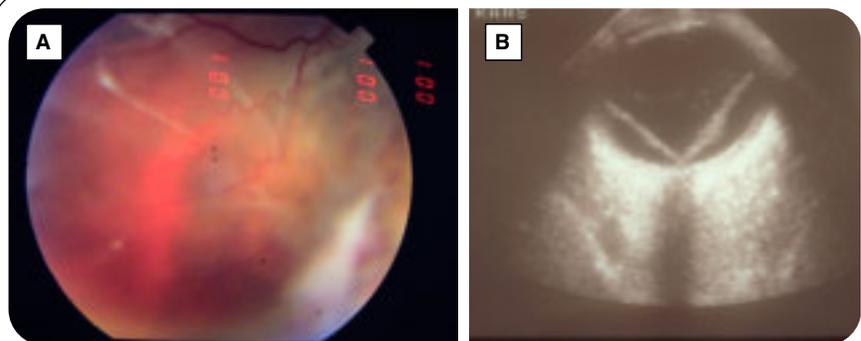


Figure 4. (A) Retinal detachment occurring in an eye treated for *Candida* endophthalmitis with systemic fluconazole. (B) Ultrasound showing fixed detached retina in patient with *Candida* endophthalmitis without vitrectomy.

systemic toxicity of AMB is a serious disadvantage. Nephrotoxicity is the main problem encountered and frequently leads to dose reduction or cessation of therapy [52]. Other side effects include hypokalemia, fever and severe hypotension.

Lipid formulation of AMB aims to optimize therapy with AMB as these compounds are associated with fewer side effects, greater therapeutic index and higher distribution of the drug to infected tissues [53,54]. In addition, they may have better intraocular penetration than standard AMB. Goldblum and colleagues studied the ocular penetration of two different types of lipid formulated AMB, namely, AMB lipid complex (ABLC) and liposomal AMB (L-AMB), as compared with D-AMB in a rabbit model. Results showed that, after intravenous administration, AMB concentration in the aqueous and vitreous humor was highest with L-AMB in inflamed eyes. After 1 week of treatment, the AMB concentration in the vitreous was $0.47 \pm 0.21 \mu\text{g/ml}$ with L-AMB, $0.27 \pm 0.18 \mu\text{g/ml}$ with ABLC and $0.16 \pm 0.04 \mu\text{g/ml}$ with D-AMB. Intraocular distribution was highly dependent on the presence of intraocular inflammation and no intravitreal AMB was detected in the absence of uveitis [55]. In practice, AMB is injected directly into the vitreous in most patients with *Candida* endophthalmitis to bypass the blood–retinal barrier, and is not given systemically to treat intraocular infection.

The 5-flucytosine antimetabolite selectively inhibits fungal cell division. It is well absorbed orally and, although it may be administered by intravenous infusion, it is associated with higher toxicity and should only be used if the oral route is not available. After uptake into fungal cells, the drug is deaminated into 5-fluorouracil and then phosphorylated into 5-fluorodeoxyuridine monophosphate, which in turn inhibits the enzyme thymidylate synthetase, which is needed for DNA synthesis [56]. As the deamination step required for its activation occurs specifically inside fungal cells, systemic toxicity of the drug is usually low. However, bone marrow depression and alteration of liver function may be encountered. 5-flucytosine achieves therapeutic concentrations in the vitreous and aqueous humor after oral administration [57] and is active against *Candida* and *Cryptococcus* spp. and some strains of *Aspergillus* spp. It is usually used in combination with other antifungal agents as acquired resistance develops quickly if used alone. Concurrent therapy with AMB and 5-flucytosine is synergistic and can be used in severe cases of endophthalmitis [58].

Fluconazole is a triazole antifungal agent that works by inhibiting the fungal enzyme cytochrome P450, which is involved in the synthesis of ergosterol. As a result, ergosterol synthesis decreases and 14α -methylated sterols accumulate, with increase in the cell membrane permeability and, subsequently, cell death [59]. The drug is active against most yeasts, including *C. albicans*, *C. parapsilosis* and *C. tropicalis*. *C. glabrata* has reduced susceptibility to fluconazole with rates of resistance to itraconazole and fluconazole at 10.7 and 15.2%, respectively [1], while isolates of *C. krusei* are intrinsically resistant to fluconazole [60]. Fluconazole achieves good concentrations in the cerebrospinal fluid, and vitreous and aqueous

humor after oral or intravenous administration [49,59,61]. In contrast to AMB, this drug is well tolerated by most patients, with fewer side effects, but hepatotoxicity may rarely be seen, especially in patients with AIDS [62,63].

In a meta-analysis of several prospective studies that compared fluconazole with AMB, Kontoyiannis and colleagues proved that there was little difference in efficacy in the treatment of systemic candidiasis due to *C. albicans* [64]. However, given the superior penetration of this azole into the vitreous, it is the preferred systemic drug for the treatment of intraocular candidiasis [50,51]. Although fluconazole has been used for the treatment of systemic *Candida* infection for more than a decade, increasing drug resistance does not appear to pose a significant problem [1,65]. In patients with candidemia, less than 1% of fungal isolates exhibited resistance to fluconazole, with little difference in the susceptibility to fluconazole in 1999–2000 (97.9%) compared with that detected in 1994–1995 (94%) [1]. Resistance of *C. albicans* to fluconazole is currently estimated to be less than 5% [65]. Although it was originally suggested that there was a deleterious interaction between fluconazole and AMB in an animal model, studies in humans have indicated that combined therapy with fluconazole and AMB is not antagonistic compared with fluconazole monotherapy and may be associated with an improved outcome [66,67].

Ketoconazole and itraconazole are drugs that belong to the triazole and imidazole groups, respectively. Both drugs can be administered orally and are effective against *Candida* spp., but isolates of *C. glabrata* may be resistant to itraconazole [19,68]. These agents are used in mucocutaneous disease, but variable absorption and blood levels make them unreliable in the management of systemic candidiasis. Itraconazole has good activity against *Aspergillus* spp., unlike ketoconazole and fluconazole [69]. Savani and colleagues studied the ocular penetration of several azole compounds in an animal model and showed a greater ocular distribution of fluconazole than both itraconazole and ketoconazole. For all three drugs, intravitreal concentrations were higher in inflamed eyes compared with eyes with no induced uveitis [70].

Intravitreal therapy

The rationale for the use of intravitreal injections of antifungal agents is to achieve a high intraocular level of the drug and simultaneously limit drug-related systemic toxicity. Drawbacks of this modality include the likelihood of retinal toxicity and injury to intraocular structures. Furthermore, as fungal endophthalmitis is usually part of a systemic infection, intravitreal injections alone are insufficient to manage the systemic candidiasis, but are used in addition when the eye is involved.

AMB is the most common antifungal agent given by this route, although other antifungal agents have been investigated for intravitreal injection [71–74]. The recommended dose of AMB is 5–10 μg in 50–100 μl [75]. Since the drug can cause focal retinal necrosis, injection should be carried out slowly into the central vitreous cavity and as far as possible from the retinal surface [76]. The number of injections needed is not

standardized but depends mainly on the severity of infection, the clinical response of the patient to initial treatment and whether vitreous has been removed or not, since ocular clearance of the drug is enhanced after vitrectomy [77]. Although fluconazole can be given intravitreally (100 µg) and scleral implants containing fluconazole were found to be useful in a rabbit model, neither are used in most clinical centers [78].

Newer azole drugs

Voriconazole is a new-generation triazole, approved recently for the treatment of serious infection by *Aspergillus*, *Fusarium*, *Paecilomyces* spp. and resistant *Candida* spp. [79]. The drug has an excellent pharmacokinetic profile with 96% oral bioavailability and achieves a peak plasma concentration in 2–3 h after oral dosage [80]. In one study, after two oral doses (400 mg, administered 12 h apart), aqueous and vitreous levels were found to be greater than the minimum concentration required to inhibit 90% of growth (MIC₉₀) of most fungi with the concentrations in the aqueous and vitreous equal to 53 and 38.1%, respectively, of the plasma drug concentration [81].

Furthermore, in another study, 1 week of intravenous treatment with voriconazole was shown to result in higher intraocular concentrations and achieved a level exceeding 18-times the MIC₉₀ of *C. albicans* [15]. Voriconazole use may be associated with skin rash and photosensitivity as well as disturbance of liver function. Importantly, when this is given systemically, transient visual disturbances (photopsia, disturbed color vision and blurring of vision) are seen in approximately a third of the patients with no evidence of ocular involvement, but these are reversible and do not necessitate drug withdrawal [82].

In an *in vitro* study of the susceptibility of pathogens causing fungal keratitis and endophthalmitis in South Florida, Marangon and colleagues found that nearly all isolates were sensitive to voriconazole, while susceptibility to AMB and fluconazole was 76.5 and 60%, respectively. For *Candida* spp., MIC₉₀ values for voriconazole were much lower than that of AMB (0.5 µg/ml), fluconazole (0.5 µg/ml) and others. In this study, *Candida* spp. were the most common cause of endogenous endophthalmitis, with *C. albicans* responsible for 53.5% of the *Candida* cases [13]. Breit and colleagues published a review series of five patients with endogenous *Candida* endophthalmitis who were managed successfully with systemic voriconazole alone or in combination with caspofungin. Only one patient with bilateral disease experienced treatment failure that necessitated intravitreal AMB in either eye, although three of these patients had organisms that were resistant to systemic fluconazole [15].

Voriconazole has been considered recently for intravitreal injection. Gao and colleagues investigated the safety of injecting the drug into the vitreous of a rodent model [83]. Their data showed that intravitreal concentrations of 25 µg/ml or less were not associated with any retinal toxicity that could be detected by electrophysiological and histological examination. They suggested that a dose of 100 µg could be used safely for intravitreal injection in humans [83]. In the paper by Breit and

colleagues, one patient with severe *C. albicans* endophthalmitis was treated successfully with intravitreal in addition to systemic voriconazole and no sign of retinal toxicity was seen up to 4 months postinjection [15]. Several other reports have also demonstrated the safety and efficacy of intravitreal voriconazole in cases of fungal endophthalmitis due to *Aspergillus* and *Verticillium* spp. [84–86].

Posaconazole is a new triazole antifungal agent currently being investigated for treating systemic mycotic infections [87,88]. The drug has an extended spectrum against most fungal pathogens, including fluconazole-resistant *Candida* and refractory cases of *Fusarium* and *Aspergillus* infection [89]. Posaconazole has excellent bioavailability after oral administration and appears to achieve high concentrations in both aqueous humor and vitreous [87,90]. To date, the exact role of posaconazole in treating intraocular fungal infection has not been determined. Sponself and colleagues published the report of a patient with contact lens-related *Fusarium solani* keratitis and endophthalmitis that resolved completely with systemic and topical posaconazole, despite being resistant to AMB and ketoconazole [90].

Echinocandins

Caspofungin belongs to a new class of antifungal agents known as echinocandins, which selectively target the fungal cell wall [91]. The drug is approved currently in the USA and Europe for the treatment of invasive aspergillosis resistant to AMB and itraconazole and can only be given parenterally.

In a prospective trial comparing caspofungin and AMB for the treatment of invasive candidiasis, both drugs were shown to be equally effective. No patients in the caspofungin group and only one patient in the AMB group developed new ocular lesions while receiving treatment. Fewer drug-related side effects were experienced by patients receiving caspofungin [92].

Several animal studies have demonstrated excellent drug distribution into the eye of the related drug micafungin after systemic administration [93]; however, clinical experience with caspofungin in endophthalmitis is limited. Few case reports describe its use in individual cases of *C. glabrata* and *Fusarium* endophthalmitis, whether alone or combined with other antifungal agents [14,84]. As discussed previously, Breit and colleagues achieved good results with a combination of voriconazole and caspofungin in a series of patients with endophthalmitis due to *C. albicans*, *C. glabrata* and *C. guilliermondii* [15]. Other drugs from this group are emerging [94].

Intravitreal steroids

The use of intraocular steroid injection in the management of fungal endophthalmitis is controversial, but is not undertaken by most ophthalmologists. Although in an animal study, Coats and Peyman showed that injecting dexamethasone in the vitreous increased significantly the rate of vitreous clearance when combined with AMB [95], clinical use in cases of exogenous fungal endophthalmitis failed to show any significant difference in visual or anatomical outcome in the dexamethasone-plus group [96]. In addition, steroids may interfere with monocyte

cell activity on fungal pathogens that may potentiate the infection [97]. No controlled trial data exist, and it is unlikely that such a trial would be undertaken.

Ocular surgery

Surgical removal of the vitreous gel (vitrectomy) is indicated in eyes with fungal endophthalmitis that have severe vitreous involvement. Early vitrectomy may be indicated for lesions involving the fovea and also in patients with poor visual acuity at presentation. Vitrectomy is typically both diagnostic and therapeutic in patients with *Candida* infection. Removal of the vitreous decreases the fungal load and thus increases the effect of the antifungal drugs and provides a specimen for laboratory studies and culture. Most surgeons would opt to inject an antifungal drug intravitreally at the conclusion of the surgery [36]. In addition, vitrectomy decreases the late-onset development of retinal membranes and tractional retinal detachment due to vitreous contraction that can occur during the healing stage (FIGURE 4) [98]. Rarely, choroidal neovascularization may complicate *Candida* endophthalmitis and can result in late-onset visual loss. Management is with laser photocoagulation or surgical excision [99,100].

Outcome

Visual prognosis in endogenous endophthalmitis depends on the virulence of the organism, the location of the fungal abscess and the degree of ocular damage before the start of effective treatment [16]. Retinal detachment consequent to vitreous contraction in nonvitrectomized eyes and the development of fibrotic membranes distorting the macula are an important cause of visual loss after settling of the infection. In addition, choroidal neovascular membranes may develop at the site of healed scars. Patients with *Candida* endophthalmitis generally have a better visual outcome than those due to *Aspergillus* infection, which tend to involve the macula and are usually associated with more extensive retinal damage [17,30,41]. In two reports, more than 80% of patients with *Candida* endophthalmitis had a final visual acuity of 6/60 or more [19,30], with better visual acuity in eyes that underwent early vitrectomy and intravitreal injection of antifungal drugs [36,101]. It is important to remember that patients with candidemia have a high overall mortality rate, which may approach 50% [101,102], which reflects the extent and severity of fungal infection, as well as their underlying medical problems [41].

Conclusions

Candida chorioretinitis is the most common cause of endogenous endophthalmitis seen in clinical practice. Although uncommon, the disease is serious and frequently sight threatening. All but a few cases of ocular candidiasis are seen in patients with risk factors for candidemia, and thus, they are at risk of death due to concomitant infection of vital organs, such as the heart or brain. Important predisposing factors for systemic candidemia include systemic immunosuppression, recent invasive procedures and intravenous drug abuse. Although *Candida* is an increasingly prevalent cause of nosocomial infection, the

incidence of ocular infection appears to be decreasing owing to the recent trend of early systemic treatment of deep tissue fungal infection and prophylaxis with fluconazole in high-risk situations. Typically, the disease presents as a focal white fluffy infiltrate in the choroid and retina that may break into the vitreous. Lesions are usually associated with vitritis and vitreous abscesses may be seen. The diagnosis is usually made on clinical grounds and requires a high index of suspicion. It may be confirmed by laboratory investigation, but the yield of positive blood and vitreous cultures is generally low. Both intravitreal and systemic treatment are used for treatment of *Candida* chorioretinitis and endophthalmitis, but still there is no universal agreement regarding the specific indications for either form of treatment. Systemic antifungal drugs are needed to manage coexisting candidemia and preference is given to drugs that penetrate the blood–retinal barrier when lesions extend into the retina and vitreous. Vitrectomy and intravitreal AMB are indicated for cases with severe vitreous involvement. Early vitrectomy appears to decrease the incidence of late retinal detachment and improve the visual outcome. Intravitreal voriconazole may offer a new treatment option to manage *Candida* endophthalmitis but further evaluation is needed.

Expert commentary

Candida chorioretinitis should be considered in the differential diagnosis of posterior uveitis or endophthalmitis in an immunocompromised host or a patient who has recently had intravenous lines or is an intravenous drug abuser. The diagnosis is usually straightforward on clinical examination, but vitreous biopsy or, preferentially, a diagnostic and therapeutic vitrectomy may be needed in selected patients to confirm or rule out the diagnosis. Although not available routinely, PCR studies of vitreous specimens appear to be very sensitive and can compensate for the shortcomings of vitreous and aqueous humor cultures. Successful management depends on early diagnosis and prompt treatment, as well as close collaboration between physicians and ophthalmologists. All patients with candidemia should have a formal ophthalmological assessment. When visual symptoms or a red eye are present, this is urgent. In the absence of ocular symptoms, ocular examination should occur within 1–2 weeks. Repeat evaluation at 2 weeks is required in patients seen initially within a few days of a positive blood culture. Management is usually tailored to the degree and severity of ocular involvement. Early lesions confined to the choroid are outside the blood–retinal barrier and can be treated as for systemic infection with drugs, such as AMB. Flat lesions involving the retina with minimal overlying vitritis need initial systemic treatment with drugs, such as fluconazole, that achieve a high therapeutic level in the eye and also need to be watched carefully. Fluconazole can be used without deleterious drug interaction with AMB when systemic involvement necessitates continuing AMB. Lesions extending into the vitreous are best managed with vitrectomy and intravitreal AMB injection in addition to systemic fluconazole. Voriconazole should be considered for the management of ocular candidiasis in the following situations: fungal isolates

from blood/eye that are likely to be or known to be not susceptible to fluconazole, especially when resistance is demonstrated by *in vitro* testing, as with *C. krusei* and *C. glabrata* and patients who develop intraocular involvement while receiving a full systemic treatment dose of fluconazole. Caspofungin and emerging echinocandins should be considered as salvage therapy or if toxicity prevents the use of other agents [103].

Five-year view

The area that will be the focus of most research activity during the next 5 years is probably the development of new systemic agents that can penetrate the blood–retinal barrier and achieve high therapeutic levels in the vitreous, perhaps avoiding the need for additional intravitreal therapy. Voriconazole appears to

be promising but further trials are needed before it should replace fluconazole as systemic treatment for fungal endophthalmitis, which is cheaper, more readily available and has stood the test of time. The role of caspofungin remains uncertain at the present time.

Further development of intravitreal medications continues and newer drugs will be coming into clinical practice. Attention should also be given to the analysis of the pathophysiology during the healing process of *Candida* endophthalmitis, as clinical experience shows that retinal traction due to formation of surface membranes remains an important cause of visual failure in treated eyes. Development of therapeutic agents that modulate cellular activity and extracellular matrix proliferation could, at least theoretically, improve the visual outcome.

Key issues

- *Candida albicans* is the most common cause of fungal endogenous endophthalmitis.
- *Candida* endophthalmitis is seen mainly in immunocompromised patients, after invasive medical procedures and in intravenous substance misusers.
- Neutrophils appear to be the most important defensive mechanism against dissemination of *Candida* infection and this may explain the low incidence of *Candida* retinitis in AIDS patients with severe immunosuppression.
- All patients with candidemia should have a dilated ophthalmological examination shortly after diagnosis for early detection of ocular involvement.
- Diagnosis is mainly clinical and treatment requires cooperation with other physicians involved in the management of the patient.
- The sensitivity of standard cultures for the detection of *Candida* in the vitreous is still relatively low and candidemia may be intermittent, thereby remaining undetected by blood cultures.
- PCR of aqueous and vitreous samples is a recent method that may become useful in patients with an unclear diagnosis.
- Incidence is decreasing owing to the trend of prophylaxis in patients at high risk and early initiation of antifungal agents in patients with systemic candidiasis.
- Fluconazole remains the systemic drug of choice for intraocular candidiasis as it crosses the blood–retinal barrier and is effective against most of the endophthalmitis-causing *Candida* spp.
- Early vitrectomy and intravitreal antifungal agents appear to improve the visual prognosis.
- Further studies are needed to define the indications for the newer antifungal agents.

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