The eye in systemic sepsis

Aldrin Khan, Narciss Okhravi and Susan Lightman

Aldrin Khan
MBBS (UWI)
Narciss Okhravi
PhD FRCOphth
Susan Lightman
PhD FRCP FRCOphth
Department of Clinical Ophthalmology, Institute of Ophthalmology, Moorfields Eye Hospital, London

Clin Med JRCPL 2002;**2**:444–8

ABSTRACT – Metastatic or endogenous endophthalmitis (EE) is a serious consequence of systemic sepsis. It is defined as intraocular infection resulting from haematogenous spread of organisms in which the initial focus of infection is at a site distal to the eye. A red/sore eye in a patient with a known septic focus needs urgent attention as EE can be a major cause of visual loss. Early diagnosis and treatment are associated with better visual outcome. This article focuses on the two main causes of EE, namely bacterial and fungal infections, and also briefly mentions dissemination of cytomegalovirus to the eye in immunocompromised patients. Although conscious patients may notice an ocular problem, unconscious or very sick patients may not; vigilance by medical staff in looking for early signs of this is extremely important.

KEY WORDS: candida, ciprofloxacin, cytomegalovirus (CMV), endophthalmitis, floaters, hypopyon, red eye, retinal infiltrates, retinitis, septicaemia

Endogenous fungal endophthalmitis

Fungal sepsis is identified most frequently in hospitalised patients who are seriously ill. Endogenous fungal endophthalmitis (EFE) occurs in 28–45% of patients with candidaemia[1,2,3] and is the most common form of endogenous endophthalmitis (EE)[4]. Patients usually present with floaters and decreased vision, unilateral or bilateral. Onset is often insidious; in its early stages EFE can be asymptomatic[2], but if left untreated can have devastating consequences for visual function. Therefore, regular screening of high risk cases is undertaken in many centres[5,6]. High risk characteristics include those listed in Table 1.

Table 1. Some of the high risk characteristics in the presence of which routine screening should be undertaken.

- intravenous drug abuse (lemon juice containing candida spp is used to dissolve heroin prior to injection)
- neutropenia
- prolonged use of broad spectrum antibiotics
- immunosuppressive therapy and chemotherapy
- prolonged use of indwelling central lines
- primary or secondary immunodeficiency (eg bone marrow transplant/ leukaemic patients
- chronically ill or debilitated patients (eg meningitis, chronic renal failure, malignancy, AIDS)
- premature infants[7,8]

Candidiasis

Candida albicans is the most common pathogen causing EFE and in some series is the causative agent in 85–99% of all cases[6,9]. Non-albicans candida spp are important as aetiological agents[10] because fungaemia with these species is associated with a higher incidence of endophthalmitis than with *C. albicans*[11]. Other causes of EFE in descending order of importance are *Aspergillus fumigatus*, cocciodioides, cryptococcus, fusarium, histoplasmosis and paecilomyces[4].

Diagnosis of ocular candidiasis. The clinical diagnosis of ocular candidiasis is largely made on the ocular appearance[8]. The organism typically causes inflammation in the choroid and retina, with subsequent spread into the vitreous cavity[8]. The ophthalmoscopic appearance is of one or more creamy-white, usually round and sometimes elevated retinal lesions, often sited in the posterior pole of the eye (Fig 1). They may vary in size from small pinpoint lesions to two-disc diameter in width[8]. If the vitreous is involved, multiple clumps may form ('puff balls') (Fig 2). Thread-like strands may connect these, producing a so-called 'string of pearls' appearance.

Ocular lesions can indicate otherwise occult deep tissue fungal infection and are useful indicators of systemic candidiasis[12,13]. Although autopsy studies have demonstrated a high incidence (78%) of ocular involvement in patients with candidaemia[12], the eye can be the only organ involved[8]. Conversely, only 11% of patients with endophthalmitis have had documented systemic fungal infection[9]. In disseminated candidiasis, haematogenous spread occurs early in the disease, most commonly to the eye, kidney, liver, spleen and skin with resultant abscess formation at these sites[12]. The diagnosis of fungaemia can be difficult as it is usually transient and blood cultures are relatively insensitive[9,14,15]. Patients in whom multiple blood cultures are positive have a greater incidence of EFE[9]. Positive fungal cultures from a deep body site also increase the risk (19 times) of fungal endophthalmitis[6].

Treatment of endogenous fungal endophthalmitis

Patients have been successfully treated with:

- systemic antifungal therapy alone[7,16,17]
- intravitreal amphotericin B alone[15,18,19,20], or
- vitrectomy with or without intravitreal amphotericin B and with or without systemic antifungal agents[21–23].

Most ophthalmologists would agree, however, that involvement of the vitreous in the disease process warrants consideration of vitrectomy to prevent retinal detachment occurring in these eyes[8,23–25].

Systemic disease

Treatment of systemic disease includes the following:

- Amphotericin B is often given intravenously (iv). It does not achieve adequate therapeutic levels inside the eye[26], although resistance is rare.
- 5-Fluorocytosine can be given orally, causes few adverse reactions and penetrates well into the eye[27]. It is rarely used in isolation as resistance has been reported in up to 53% of cases[28].
- The azoles, in particular fluconazole, also penetrate well into the eye, have good absorption following oral administration and few adverse effects[29].

The most common management for EFE involves intravitreal injection of amphotericin B (5–10 μg in 0.1 ml) with systemic fluconazole and vitrectomy if the vitreous cavity is involved. Although resistance to azoles is uncommon, care should be taken when a non-albicans candida spp is isolated as their sensitivities may be different[11].

Visual prognosis

Visual prognosis is determined by the location of the retinal abscess and time from onset to treatment. Brod *et al*[15] reported that 80% of cases with less than two months from onset to treatment had 20/50 or better vision at six months, whereas those whose treatment was delayed by more than two months were all worse than 20/80.

Infection with *A. fumigatus* carries a poorer visual prognosis than with *C. albicans*[9]. One study[30] showed that the longer the period of time before resolution of the fungal infection, the greater the likelihood of surface membrane (epiretinal membrane) and scar formation involving the macula, and thus a poor visual outcome. In another study, 65% of 15 eyes infected with candida achieved final visual acuities of 20/400 or better, whereas all three eyes infected with aspergillus had final visual acuities worse than 20/400[9].

Another important factor in determining the final visual outcome is retinal detachment: 50% of patients in whom retinal detachment occurred had a final visual acuity of 20/400 or worse[15]. Other complications that can reduce vision include epiretinal membrane formation, choroidal neovascularisation, and cataract formation[15].

Endogenous bacterial endophthalmitis

Endogenous bacterial endophthalmitis (EBE) accounts for 2–8% of all cases of endophthalmitis[31]. It is usually associated with debilitating medical disease (eg uncontrolled diabetes mellitus[32]) and chronic renal failure, or occurs after invasive medical procedures (eg endoscopy) or major surgery. It may also occur following iv drug abuse and recent trauma to a body site other than the eye[33,34]. The disease is usually unilateral, but has been reported as bilateral in 10–25% of cases[35].

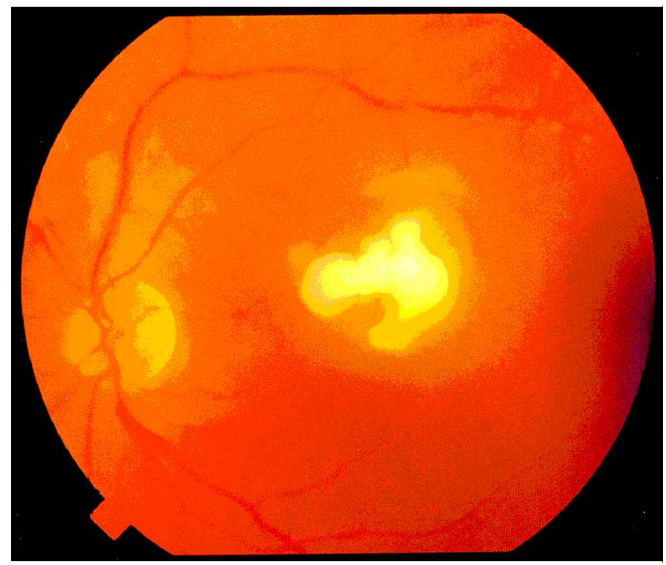

Fig 1. Macular abscess in the posterior pole in a patient with endogenous fungal endophthalmitis. *Candida albicans* was cultured from the blood of this patient.

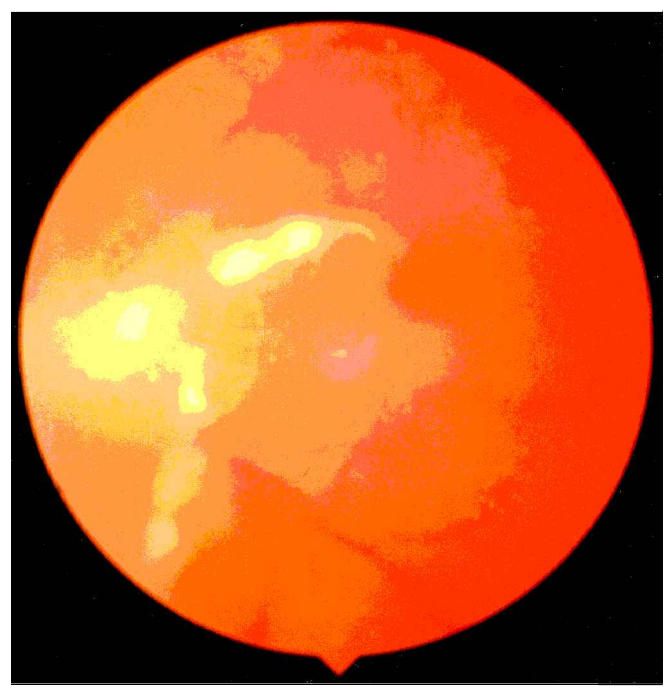

Fig 2. Puff ball/string of pearls appearance in a patient with candida endogenous fungal endophthalmitis involving the vitreous.

Key Points

- A red/sore eye, especially if the vision is reduced, in a patient with a known septic focus needs urgent ophthalmological assessment NOT antibiotic drops
- Endogenous fungal endophthalmitis occurs in 28–45% of patients with candidaemia and can destroy vision
- A wide variety of bacteria can cause endophthalmitis in a patient with bacteraemia and result in severe visual loss
- Cytomegalovirus (CMV) viraemia in an immunosuppressed patient can result in CMV retinitis
- Loss of vision occurs more frequently in all types of metastatic infection involving the eye if treatment is delayed

Unlike EFE, the onset is usually rapid, with the majority of patients developing ocular symptoms within one week. Patients complain of decreased vision, floaters, a red sore eye and headache. Some patients have associated systemic symptoms such as fever, weight loss or malaise at the time of onset of ocular symptoms. Ocular examination may reveal eyelid oedema, chemosis, conjunctival injection, corneal oedema, anterior chamber cells and flare, or a hypopyon (Fig 3), iris microabscess, absent red reflex, vitreous cell and debris, retinal infiltrates (Fig 4) and flame-shaped retinal haemorrhages with or without white centres (Roth's spot). Orbital involvement is suggested by proptosis and restricted ocular motility (known as panophthalmitis). Subretinal abscesses have been reported secondary to haematogenous spread of klebsiella spp, nocardia spp, *Pseudomonas aeruginosa*, *Streptococcus viridans*[31] and *Staphylococcus aureus*[36,37].

Once the diagnosis is suspected, the source of the infection needs to be identified if unknown. Chest X-ray, echocardiogram, blood and urine cultures are useful, together with aqueous and vitreous samples for microbiological analysis.

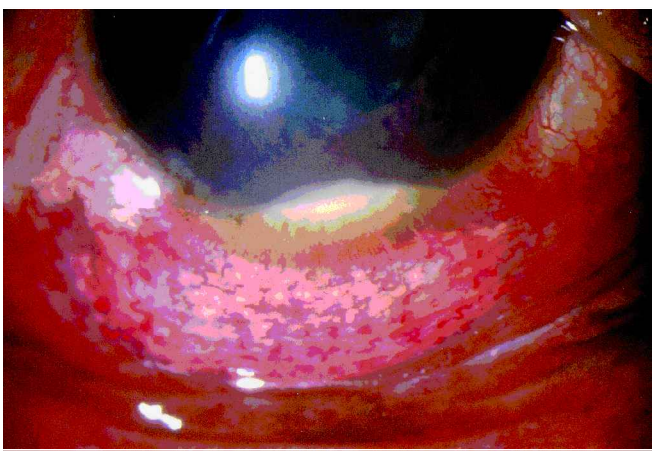

Fig 3. Hypopyon in a patient with endogenous bacterial endophthalmitis. The hypopyon consists mainly of polymorphonuclear leukocytes.

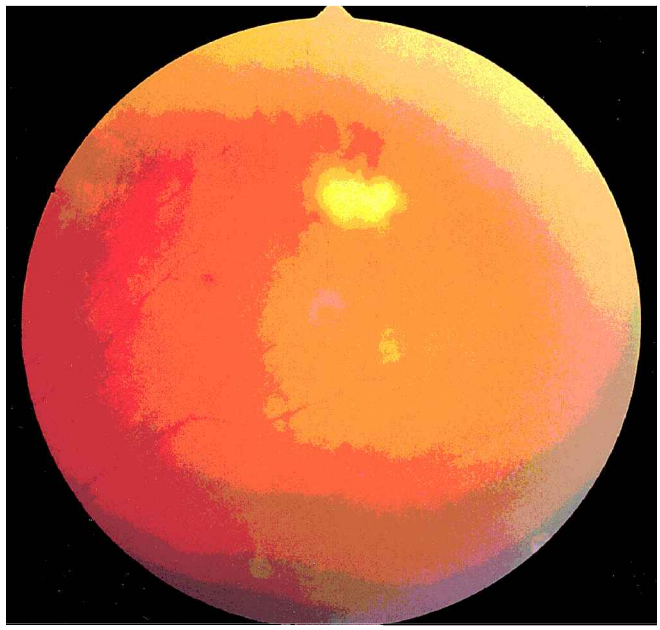

Fig 4. A single peripheral retinal abscess in a patient with endogenous bacterial endophthalmitis.

Treatment of endogenous bacterial endophthalmitis

Collection of intraocular fluids is followed by injection of broad spectrum antibiotics into the vitreous (such as vancomycin 2.0 mg in 0.1 ml and amikacin 0.4 mg in 0.1 ml). Topical antibiotics and often steroid drops are commenced immediately, together with systemic antibiotics. Few antibiotics given systemically other than ciprofloxacin achieve therapeutic levels inside the eye, so this compound is commonly used[38].

The role of systemic steroids in metastatic endophthalmitis is controversial and may not be appropriate in a debilitated patient, but they are often useful in reducing the associated inflammatory response inside the eye.

Identification of microorganisms

Okada *et al*[35] have demonstrated a 96% identification rate of organisms obtained from at least one body fluid, and positive cultures from 74%, 72%, 60% and 30% vitreous, blood, aqueous and urine samples, respectively. Most organisms causing EBE are Gram-positive (66% in one case series)[35]. Organisms include *S. aureus*, *S. viridans*, bacillus spp (common in iv drug abusers), *Neisseria meningitidis*, *Haemophilus influenzae*, salmonella spp[39] (in immunocompromised patients), *Clostridium septicum* and, rarely, capnocytophaga spp.

The most common presumptive source of EBE has been reported as infectious endocarditis, followed by gastrointestinal and genitourinary tract infection[35]. One series from Taiwan of 180 consecutive patients with a pyogenic liver abscess (whatever the organism) found a 1.7% incidence of metastatic endophthalmitis, rising to 5.2% in patients with a liver abscess due to klebsiella and 8% when there was added evidence of klebsiella

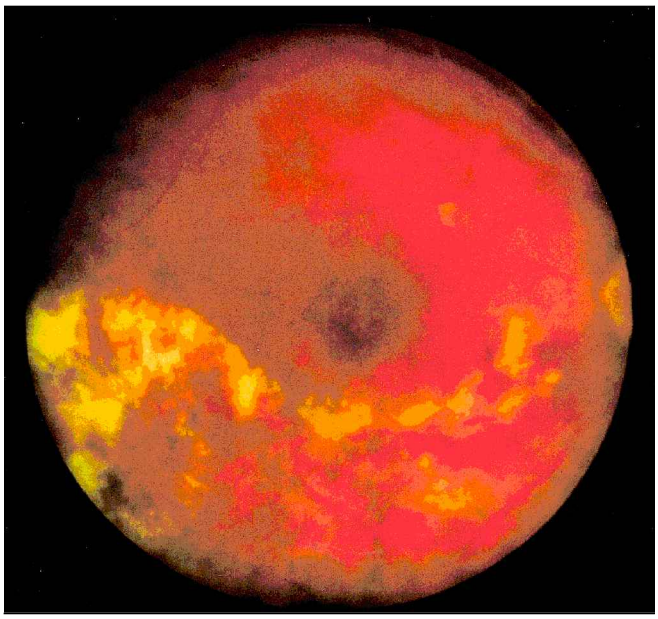

Fig 5. Cytomegalovirus (CMV) retinitis in an immunosuppressed patient with CMV viraemia. Note the characteristic haemorrhage, exudate and necrosis along the retinal vessels (in one quadrant in this case) often described as a 'pizza pie' appearance.

bacteraemia[36]. In four patients with EBE from either pneumococcal or meningococcal infection, both endocarditis and meningitis were found[35]. Multi-organ involvement should therefore be considered, and management altered as required.

Management of endogenous bacterial endophthalmitis

Management of patients with EBE requires an early aggressive approach to achieve the best visual outcome. Factors influencing the outcome of treatment include:

- diagnostic delay
- type of organism involved
- timely treatment[35],
- initial presenting visual acuity
- the presence of retinal detachment.

In one study of 28 patients, 22 had a final visual acuity of 20/400 or worse and eight patients had the infected eye enucleated due to poor response to treatment, corneal perforation or intractable pain[35].

Cytomegalovirus retinitis in the immunocompromised host

Patients who are immunosuppressed either by disease or medication can lose the normal immune control of cytomegalovirus (CMV) replication and develop CMV viraemia and disease[40]. They may present with systemic symptoms such as fever, anorexia and malaise, but can also develop pneumonitis, hepatitis, gastrointestinal ulceration, encephalopathy and chorioretinitis, all of which have a high morbidity or mortality[41]. Untreated CMV retinitis is slowly and relentlessly progressive, resulting in blindness from posterior pole involvement or retinal detachment. The patients may present with blurred vision and floaters but may also be asymptomatic.

Ocular examination usually reveals a white uninflamed eye with areas of whitening and haemorrhage in the retina either unilateral or bilateral (Fig 5). The diagnosis is usually made on the history and clinical appearance, although polymerase chain reaction for CMV/DNA of vitreous fluid is valuable in confirming the diagnosis especially when the clinical features are not classic.

Management of cytomegalovirus retinitis

Management is aimed at reducing both the systemic immunosuppression, where possible, and the circulating CMV load with iv antiviral agents such as ganciclovir. The retinitis can be managed with systemic ganciclovir, but additional therapy may be given into the vitreous[42–44].

Conclusion

Sick patients who are known to have an infective focus or are at risk of sepsis, who complain of eye problems or have a red eye must undergo ophthalmological assessment. Collaboration between different specialties is crucial in managing patients with intraocular infection. Not only can the visual outcome of endogenous endophthalmitis be poor but the associated septicaemia may be life-threatening, with up to 15% of patients dying during the course of the disease[9,35]. These patients need to be managed aggressively with local and systemic therapy, and surgical intervention when necessary, as early diagnosis and treatment are associated with a better visual outcome.

References

1 Brooks RG. Prospective study of Candida endophthalmitis in hospitalized patients with candidemia. *Arch Intern Med* 1989;**149**:2226–8.

2 Parke DW 2nd, Jones DB, Gentry LO. Endogenous endophthalmitis among patients with candidemia. *Ophthalmology* 1982;**89**:789–96.

3 Bross J, Talbot GH, Maislin G, Hurwitz S, Strom BL. Risk factors for nosocomial candidemia: a case-control study in adults without leukemia. *Am J Med* 1989;**87**:614–20.

4 Samiy N, D'Amico DJ. Endogenous fungal endophthalmitis. Review. *Int Ophthalmol Clin* 1996;**36**:147–62.

5 Pizzo PA. Infectious complications in the child with cancer. I. Pathophysiology of the compromised host and the initial evaluation and management of the febrile cancer patient. Review. *J Pediatr* 1981;**98**:341–54.

6 Enzenauer RW, Calderwood S, Levin AV, Elder JE, Morin JD. Screening for fungal endophthalmitis in children at risk. *Pediatrics* 1992;**90**:451–7.

7 Johnson DE, Thompson TR, Green TP, Ferrieri P. Systemic candidiasis in very low-birth-weight infants (less than 1,500 grams). *Pediatrics* 1984;**73**:138–43.

8 Chignell AH. Endogenous candida endophthalmitis. *J R Soc Med* 1992;**85**:721–4.

9 Essman TF, Flynn HW Jr, Smiddy WE, Brod RD *et al.* Treatment outcomes in a 10-year study of endogenous fungal endophthalmitis. *Ophthalmic Surg Lasers* 1997;**28**:185–94.

10 Joshi N, Hamory BH. Endophthalmitis caused by non-albicans species of candida. Review. *Rev Infect Dis* 1991;**13**:281–7.
11 Donahue SP, Greven CM, Zuravleff JJ, Eller AW *et al*. Intraocular candidiasis in patients with candidemia. Clinical implications derived from a prospective multicenter study. *Ophthalmology* 1994;**101**:1302–9.
12 Montgomerie JZ, Edwards JE Jr, Guze LB. Synergism of amphotericin B and 5-fluorocytosine for candida species. *J Infect Dis* 1975;**132**:82–6.
13 Piek JJ, Knot EA, Schooneveld MJ, Rietra PJ. Candidemia, look at the eyes. *Intensive Care Med* 1988;**14**:173–5.
14 DeGregorio MW, Lee WM, Linker CA, Jacobs RA, Ries CA. Fungal infections in patients with acute leukemia. *Am J Med* 1982;**73**:543–8.
15 Brod RD, Flynn HW Jr, Clarkson JG, Pflugfelder SC *et al*. Endogenous Candida endophthalmitis. Management without intravenous amphotericin B. *Ophthalmology* 1990;**97**:666–72; discussion 672–4.
16 Gallo J, Playfair J, Gregory-Roberts J, Grunstein H *et al*. Fungal endophthalmitis in narcotic abusers. Medical and surgical therapy in 10 patients. *Med J Aust* 1985;**142**:386–8.
17 Sihota R, Agarwal HC, Grover AK, Sood NN. Aspergillus endophthalmitis. *Br J Ophthalmol* 1987;**71**:611–3.
18 Hogeweg M, de Jong PT. Candida endophthalmitis in heroin addicts. *Doc Ophthalmol* 1983;**55**:63–71.
19 Perraut LE Jr, Perraut LE, Bleiman B, Lyons J. Successful treatment of Candida albicans endophthalmitis with intravitreal amphotericin B. *Arch Ophthalmol* 1981;**99**:1565–7.
20 Stern GA, Fetkenhour CL, O'Grady RB. Intravitreal amphotericin B treatment of Candida endophthalmitis. *Arch Ophthalmol* 1997;**95**: 89–93.
21 Roney P, Barr CC, Chun CH, Raff MJ. Endogenous aspergillus endophthalmitis. *Rev Infect Dis* 1986;**8**:955–8.
22 Lance SE, Friberg TR, Kowalski RP. Aspergillus flavus endophthalmitis and retinitis in an intravenous drug abuser. A therapeutic success. *Ophthalmology* 1988;**95**:947–9.
23 Barrie T. The place of elective vitrectomy in the management of patients with Candida endophthalmitis. *Graefes Arch Clin Exp Ophthalmol* 1987;**225**:107–13.
24 Snip RC, Michels RG. Pars plana vitrectomy in the management of endogenous Candida endophthalmitis. *Am J Ophthalmol* 1976;**82**: 699–704.
25 Kinyoun JL. Treatment of Candida endophthalmitis. *Retina* 1982;**2**: 215–22.
26 Jones DB. Chemotherapy of experimental endogenous Candida albicans endophthalmitis. *Trans Am Ophthalmol Soc* 1980;**78**:846–95.
27 Walsh JA, Haft DA, Miller MH, Loran MR, Friedman AH. Ocular penetration of 5-fluorocytosine. *Invest Ophthalmol Vis Sci* 1978;**17**: 691–4.
28 Warner JF, McGehee RF, Duma RJ, Shadomy S, Utz JP. 5-fluorocytosine in human candidiasis. *Antimicrobial Agents Chemother* 1970;**10**:473–5.
29 Savani DV, Perfect JR, Cobo LM, Durack DT. Penetration of new azole compounds into the eye and efficacy in experimental Candida endophthalmitis. *Antimicrob Agents Chemother* 1987;**31**:6–10.
30 Christmas NJ, Smiddy WE. Vitrectomy and systemic fluconazole for treatment of endogenous fungal endophthalmitis. *Ophthalmic Surg Lasers* 1996;**27**:1012–8.
31 Harris EW, D'Amico DJ, Bhisitkul R, Priebe GP, Peterson R. Bacterial subretinal abscess: a case report and review of the literature. Review. *Am J Ophthalmol* 2000;**129**:778–85.
32 Cordido M, Fernandez-Vigo J, Cordido F, Rey AD. Bilateral metastatic endophthalmitis in diabetes. *Acta Ophthalmol (Copenhagen)* 1991;**69**: 266–7.
33 Greenwald MJ, Wohl LG, Sell CH. Metastatic bacterial endophthalmitis: a contemporary reappraisal. Review. *Surv Ophthalmol* 1986;**31**:81–101.
34 Farber BP, Weinbaum DL, Dummer JS. Metastatic bacterial endophthalmitis. *Arch Intern Med* 1985;**145**:62–4.
35 Okada AA, Johnson RP, Liles WC, D'Amico DJ, Baker AS. Endogenous bacterial endophthalmitis. Report of a ten-year retrospective study. *Ophthalmology* 1994;**101**:832–8.
36 Coll GE, Lewis H. Metastatic choroidal abscess and choroidal neovascular membrane associated with *Staphylococcus aureus* endocarditis in a heroin user. *Retina* 1994;**14**:256–9.
37 Limaye SR, Goldberg MH. Septic submacular choroidal embolus associated with intravenous drug abuse. *Ann Ophthalmol* 1982;**14**:518–22.
38 Lesk MR, Ammann H, Marcil G, Vinet B, et al. The penetration of oral ciprofloxacin into the aqueous humor, vitreous, and subretinal fluid of humans. *Am J Ophthalmol* 1993;**115**:623–8.
39 Weinstein JM, Elliott J, Tilford RH. Metastatic endophthalmitis due to Salmonella typhimurium. *Arch Ophthalmol* 1982;**100**:293–5.
40 Griffiths PD, Cope AV, Hassan-Walker AF, Emery VC. Diagnostic approaches to cytomegalovirus infection in bone marrow and organ transplantation. Review. *Transpl Infect Dis* 1999;**1**:179–86.
41 Khare MD, Sharland M. Cytomegalovirus treatment options in immunocompromised patients. Review. *Expert Opin Pharmacother* 2001;**2**:1247–57.
42 Cantrill HL, Henry K, Melroe NH, Knobloch WH *et al*. Treatment of cytomegalovirus retinitis with intravitreal ganciclovir. Long-term results. *Ophthalmology* 1989;**96**:367–74.
43 Diaz-Llopis M, Chipont E, Sanchez S, Espana E *et al*. Intravitreal foscarnet for cytomegalovirus retinitis in a patient with acquired immunodeficiency syndrome. *Am J Ophthalmol* 1992;**114**:742–7.
44 Desatnik HR, Foster RE, Lowder CY. Treatment of clinically resistant cytomegalovirus retinitis with combined intravitreal injections of ganciclovir and foscarnet. *Am J Ophthalmol* 1996;**122**:121–3.