Metastatic endophthalmitis

Endophthalmitis carries a poor visual prognosis for patients and can be a potentially blinding condition that may result in loss of the eye. Early diagnosis and prompt treatment are imperative to save the eye. Delay in diagnosis affects visual prognosis and therefore doctors should be aware of the presenting features of endophthalmitis. Urgent ophthalmic referral is advised as soon as a diagnosis is suspected.

Inflammation within the globe of the eye is termed endophthalmitis. In common ophthalmic practice endophthalmitis is usually meant as inflammation as a result of intraocular infection. Endophthalmitis carries a poor visual prognosis for patients and can be a potentially blinding condition that may result in loss of the eye. The visual outcome for patients with endophthalmitis is poor and early recognition and specialist intervention is essential. Unfortunately delay in diagnosis remains common and physicians should be aware of the presenting features of endophthalmitis.

Classification

Endophthalmitis may be classified as exogenous or metastatic (endogenous).

Exogenous endophthalmitis occurs when the infecting organism gains access to the intraocular space via the globe – this may be secondary to intraocular surgery, penetrating ocular injury or very severe infection within the cornea or periocular structures breaching the integrity of the globe. By far the commonest type of endophthalmitis occurs after cataract surgery and the incidence after cataract surgery in one meta-analysis from Power et al (1994) was estimated to be 0.13%.

Metastatic endophthalmitis is the result of bloodborne spread of infecting organisms to the globe from a site of infection elsewhere in the body, rather than any breaches in the integrity of the globe itself. As Jackson et al (2003) reported, these patients may also be systemically unwell with signs of sepsis or metastatic infection elsewhere in the body.

Causes

Bacteria may gain entry to the body through a number of routes (Lynn, 2000). Transient bacteraemia with non-pathogenic organisms is a frequent event and in otherwise healthy individuals the bacteria are quickly cleared from the blood without any sequelae. Pathogenic bacteria most often gain access through the respiratory tract, skin, gut or genitourinary tract. These organisms may cause localized disease, severe sepsis or seed to distant organs, most commonly the liver, lung or brain. The risk of bacteraemia and metastatic infection is greater in hospitalized or immunocompromised patients because of a combination of greater opportunity for access to the bloodstream and impairment in the ability of host defences to effectively clear bacteria from blood.

The eye may also be a site of metastatic infection as bacteraemic patients can develop retinal and choroidal septic emboli. In the healthy eye, the presence of tight blood–aqueous and blood–retinal barriers help to protect the interior of the globe. Organisms may gain access to the intraocular space when these barriers are faulty or damaged, either directly by the infecting organisms or as a result of impaired defensive immune mechanisms against the infecting organisms or a combination of both. However, organisms that breach the blood–ocular barriers do not always cause endophthalmitis.

Bacteraemia may lead to ocular signs without necessarily causing intraocular infection. Roth spots are white-centred retinal haemorrhages that, according to Ling and James (1998), are a result of retinal capillary rupture and subsequent repair mechanisms – the white centre of the haemorrhage being attributed to fibrin. Roth spots were classically thought to represent septic retinal emboli pathognomonic of sub-acute bacterial endocarditis. However, it is more likely that Roth spots, and some other stigmata of endocarditis such as splinter haemorrhages, are immunological phenomena mediated by immune complexes produced as a result of chronic intravascular infection. The detection of Roth spots may help to establish a diagnosis of infective endocarditis but in the absence of other signs of intraocular infection no alteration of management is needed. Roth spots may also occur in non-infectious conditions including leukaemia, anaemia, pre-eclampsia and neonatal birth trauma.

Many different pathogenic organisms can give rise to ocular manifestations or complications in addition to their more commonly known systemic features (Lynn and Lightman, 2004). This article will focus on the metastatic spread of infection through the bloodstream to the retina and discuss bacterial and fungal endophthalmitis and cytomegalovirus (CMV) retinitis in detail.

Metastatic bacterial endophthalmitis

Metastatic bacterial endophthalmitis (MBE) has been reported by Koul et al (1989) and Harris et al (2000), among others, to account for less than 10% of all cases of

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endophthalmitis. When no apparent source of infection is identified a thorough systems review of the patient must be undertaken, paying particular attention to the heart, abdomen, skin, teeth and extremities. An infection screen should be carried out including sputum, blood and urine cultures. The primary source of infection may be difficult to locate and more extensive investigations may be required, e.g. transoesophageal echocardiography, abdominal ultrasound and computed tomography. More commonly there is a history of chronic ill health (such as uncontrolled diabetes or chronic renal failure; Smith et al (1995)). Other risk factors for developing MBE include risk factors for bacterial endocarditis (e.g. cardiac valve abnormalities, artificial heart valves and dental procedures), invasive investigative or therapeutic interventions, major surgery or gastrointestinal procedures such as endoscopy, hepatobiliary infection, long-term intravenous cannulae and intravenous drug abuse. Although, the most common presumed primary source of infection has been reported as infectious endocarditis, gastrointestinal and genitourinary infections (Okada et al, 1994), multiorgan involvement should also be considered.

There is a male preponderance of MBE (Jackson et al, 2003) and it is usually a unilateral condition, although up to 25% of cases are bilateral (Okada et al, 1994). In unilateral cases, Greenwald et al (1986) reported that the right eye was infected twice as often as the left eye and put forward the idea that this was the result of a more proximal and direct arterial blood flow to the right carotid. However, Jackson et al (2003) in their literature review found the left eye to be more commonly involved.

In North America and Europe, gram-positive organisms such as *Staphylococcus aureus* and *Streptococcus* spp. are the commonest causative organisms (Greenwald et al, 1986; Okada et al, 1994; Jackson et al, 2003). Gram-positive bacteria have also been the commonest cause of bacteraemia and severe sepsis in Europe and North America (Vincent et al, 1995; Wisplinghoff et al, 2004) although it has been suggested that gram-negative bacteraemia may be increasing in the USA (Albrecht et al, 2006). In contrast Wong et al (2000) reported the East Asian experience of predominantly gram-negative organisms, especially *Klebsiella* spp. as the leading cause of MBE. The reason for this is not clear, but may be a result of the high incidence of severe *Klebsiella* infections and particularly liver abscesses in this population.

Urgent ophthalmic referral is advised as soon as a diagnosis is suspected in order to salvage any residual vision and prevent enucleation of the eye. The ophthalmologist will take aqueous and vitreous samples for microbiological investigation.

Clinical features

The majority of patients develop characteristic features within 1 week: swollen eyelids, a red painful eye with blurred or decreased vision, floaters, photophobia and headache. In the series from Jackson et al (2003) all adult patients with MBE complained of blurred vision and two-thirds had ocular pain.

Examination findings may include injected conjunctiva with or without associated chemosis, anterior chamber inflammation with hypopyon (*Figure 1*) and corneal oedema which may be secondary to raised intraocular pressure. A view of the fundus may not be possible because of the intraocular inflammation and even the red reflex may be poor or absent. All patients in the series from Jackson et al (2003) had reduced or absent red reflex and poor fundal view because of inflammation within the vitreous. The retina may show infiltrates which can develop into subretinal abscesses (Coll and Lewis, 1994) or an abscess may be seen (*Figure 2*). The diagnosis is easily missed in the unconscious patient, for example in the intensive care unit. Endophthalmitis should be considered and actively excluded in intensive care unit patients who develop a red eye, otherwise the extent of ocular involvement may not be appreciated until they wake up with severe visual loss.

Management

The penetration of most systemic antibiotics into the eye is poor and the majority of patients require a combination of intravitreal and systemic antibiotics. Topical

Figure 1. Eye with bacterial endophthalmitis with hypopyon.

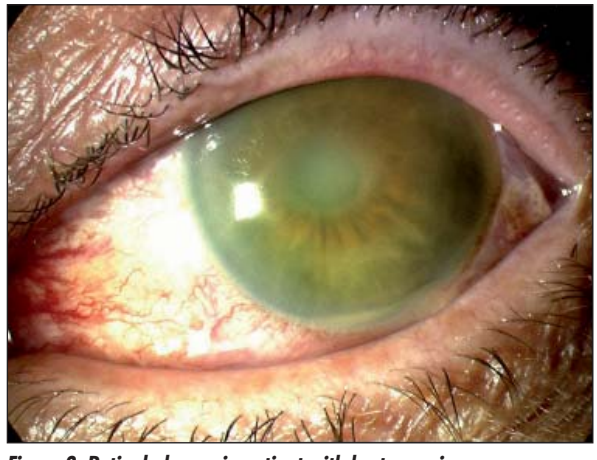
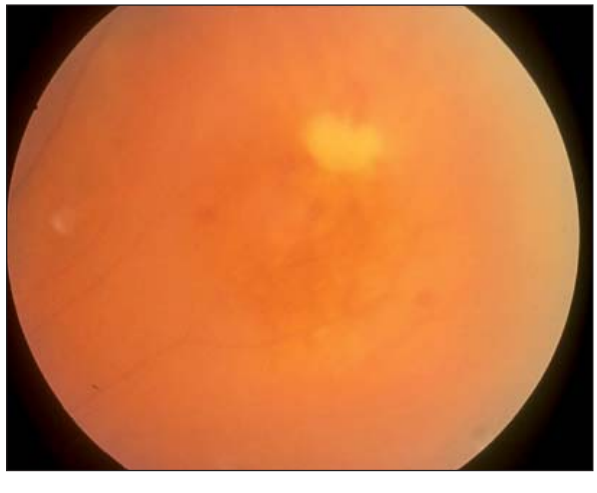


Figure 2. Retinal abscess in patient with bacteraemia.



antibiotic drops or ointment do not penetrate into the vitreous but may be indicated if there is also infection of the cornea or conjunctiva. The need to perform an intravitreal injection of antibiotics also gives the opportunity to take microbiological samples. After sampling of vitreous, broad spectrum antibiotics such as a combination of vancomycin and amikacin or ceftazidime are injected into the vitreous. These antibiotics remain in the eye for at least 24 hours and can be re-injected to provide ongoing antimicrobial activity when necessary. Systemic antibiotics should also be administered with agents that penetrate the eye such as ciprofloxacin or more recently moxifloxacin as these agents achieve therapeutic intraocular levels (Lesk et al, 1993; Hariprasad et al, 2006). These two antibiotics are also effective against many of the common infecting organisms. Topical corticosteroids are given to reduce the inflammatory process in the anterior aspect of the eye.

Intravitreal steroid use for endophthalmitis is controversial, but has been advocated by some on the basis of experimental exogenous endophthalmitis in rabbits. Maxwell et al (1991) have shown intravitreal dexamethasone helps preserve ocular architecture and can potentially lead to improved retinal function and visual benefit. Currently intravitreal steroids are not given to most patients. Systemic corticosteroids may be useful to reduce the inflammatory process but they should be used with caution in the light of the overall condition of the patient.

Jackson et al (2003) reported that eyes which had a lower perception of light or poorer vision benefited from vitrectomy in MBE. In their study, eyes that underwent vitrectomy were almost three times more likely to retain useful vision and were three times less likely to require removal of the globe or its contents. As with intravitreal steroid use, this remains controversial. Any potential benefits of vitrectomy should be weighed up against carrying out an operation in a patient who is already systemically unwell.

The main reason for visual loss is structural damage caused by the inflammatory response triggered by the infective organism. Therefore, the visual outcome depends on the infective organism, the inflammatory response mounted and the duration of untreated infection. Infection with gram-negative organisms carries a worse prognosis (Wong et al, 2000). It should also be noted that poor visual acuity at presentation is associated with poor visual outcome, highlighting the importance of early referral and diagnosis in suspected cases.

Metastatic fungal endophthalmitis

Metastatic fungal endophthalmitis (MFE) follows a period of fungaemia. MFE is more common than MBE and the most common causative species is *Candida* spp with *C. albicans* being the predominant cause (Sallam et al, 2006). Other filamentous fungi that can also give rise to MFE include aspergillus and fusarium. Predisposing factors for candidaemia include neutropenia (related to level and duration of neutropenia), prolonged stay in an intensive care unit, prolonged use of broad-spectrum antibiotics (eliminate competing microflora of the host), prolonged use of indwelling central venous lines, intravenous drug abuse, chronic debilitating illness (including malignancy, immunosuppression and immunodeficiency) and premature birth (Wright and Wenzel, 1997; Pappas et al, 2003; Wenzel and Gennings, 2005). Candidaemia has become more important as the number of patients with these risk factors has increased steadily over the past decades. *Candida* is now the fourth most common blood culture isolate in the USA and the third most common isolate in the intensive care unit (Pappas et al, 2003; Wisplinghoff et al, 2004).

MFE has previously been reported to develop in 28–45% of candidaemic patients (Parke et al, 1982; Brooks, 1989; Bross et al, 1989). More recently, MFE was reported by Feman et al (2002) to develop in only 2.5% of patients with fungaemia. This may reflect a change in practice with earlier and more effective treatment of candidaemia. The fall in *Candida* endophthalmitis may also be in part a result of the use of fluconazole, which has excellent ocular penetration, as first-line treatment for candidaemia and prophylaxis within the intensive care setting (Rex et al, 1994; Shorr et al, 2005).

Candidaemia may be transient or intermittent and patients may develop endophthalmitis without a documented positive blood culture. Thus, a high index of suspicion should be maintained if any patient with underlying risk factors for candidaemia develops a new visual symptom. All patients who have had *Candida* grown from blood culture should have a formal ophthalmic assessment as soon as possible and ideally within 2 weeks of candidaemia being detected.

Clinical features

Patients may be asymptomatic in the early stages of MFE. Common symptoms include blurred vision and floaters in one or both eyes. Anterior segment inflammation usually occurs and is more pronounced in later stages of the infection (Takebayashi et al, 2006).

The diagnosis is made largely on the characteristic fundoscopic findings on the background of candidaemia. *Candida* lesions are typically located in the choroid and retina before spreading into the vitreous. The lesions may be solitary or multiple, well-circumscribed, round and creamy-white in appearance (*Figure 3*). Vitreous involvement leads to the formation of white clumps which may be interconnected like a 'string of pearls' floating within the vitreous.

Management

Visual prognosis is dependent on three factors: extent of damage to the eye before treatment is initiated, the location of fungal lesions (i.e. if the optic nerve or macula are affected) and whether secondary retinal detachment occurs.

Early detection and treatment is the key to maintaining useful vision in these patients (Takebayashi et al, 2006). Choroidal *Candida* lesions lie outside of the blood–retinal barrier. Antifungal treatment is with either amphotericin B or fluconazole as for systemic *Candida* infection. A meta-analysis from Kontoyiannis et al (2001) showed no difference in effectiveness between the two drugs, but fluconazole has fewer adverse effects. Systemic amphotericin B, unlike fluconazole, does not achieve therapeutic levels inside the eye and thus should not be used alone if the vitreous is involved. In fungal endophthalmitis amphotericin B is usually given intravitreally where it achieves high therapeutic levels and also avoids any side effects of systemic administration.

Spread of infection into the vitreous may give rise to vitreous contraction and tractional retinal detachment. For this reason vitrectomy has been advocated (Smiddy, 1998) with the additional benefit of being able to inject amphotericin B directly into the vitreous cavity at the time of surgery.

Two new antifungals appear promising agents in the treatment of fungal infections: voriconazole and caspofungin (Laverdiere et al, 2002). Voriconazole is a new generation triazole which, when administered orally, achieves therapeutic intraocular levels. Caspofungin is the first approved agent in a new class of antifungal drugs – the echinocandins. Both these drugs are reported to be effective in systemic infections. A case series from Breit et al (2005) has shown promising results in the treatment of fungal endophthalmitis with these two agents. It is important to note that in a dose escalation study by Lazarus et al (2002), the use of oral voriconazole was associated with mild reversible visual disturbances such as blurred vision and photopsia. Treatment discontinuation was not required and the drug was otherwise well tolerated.

Cytomegalovirus

Primary infection with CMV in healthy patients can lead to an illness similar to glandular fever. In the immunocompetent host CMV rarely causes severe organ damage and CMV retinitis has not been described. However, primary CMV infection may be much more severe in immunocompromised hosts, whether this state is caused by disease or iatrogenic in origin. More commonly, however, CMV disease in the immunocompromised patient is caused by reactivation of virus. In immunocompromised hosts, the virus replicates, leading to viraemia and spread to many organs, including the eye (Jacobson and Mills, 1988). Patients with ocular CMV infection may be asymptomatic, but usually present with a history of blurred vision, and floaters and on occasion scotomata.

If left untreated, CMV retinitis progresses slowly to full thickness retinal necrosis and eventually permanent loss of vision. The diagnosis is a clinical one, with a classical fundal appearance (*Figure 4*). Diagnosis may be confirmed by polymerase chain reaction of vitreous samples. Effective anti-CMV drugs include ganciclovir, valganciclovir, foscarnet and cidofovir (Biron, 2006). These agents may be given systemically, intravitreally or via both routes. Intravitreal treatment is warranted where the site of CMV retinitis is threatening vision, i.e. close to the macular or optic nerve. Intravitreal therapy is very effective at controlling the retinitis but systemic therapy must be given at the same time to treat possible CMV in other sites and to protect the contralateral eye.

Vanganciclovir is now the preferred systemic agent as very good blood levels are achieved following oral administration. Foscarnet and cidofovir must be given parenterally and have greater toxicity than valganciclovir (Biron, 2006). The aim of initial treatment is to reduce the systemic viral load, but relapse or progression may occur if immune function is not improved (Holland and Shuler, 1992). In patients with human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), for example, CMV retinitis requires continuous suppressive therapy until treatment of the underlying HIV infection has led to sufficient immunorestoration to allow withdrawal of the anti-CMV therapy (Deayton and Griffiths, 2000).

Figure 3. Typical fundus appearance of Candida endophthalmitis.

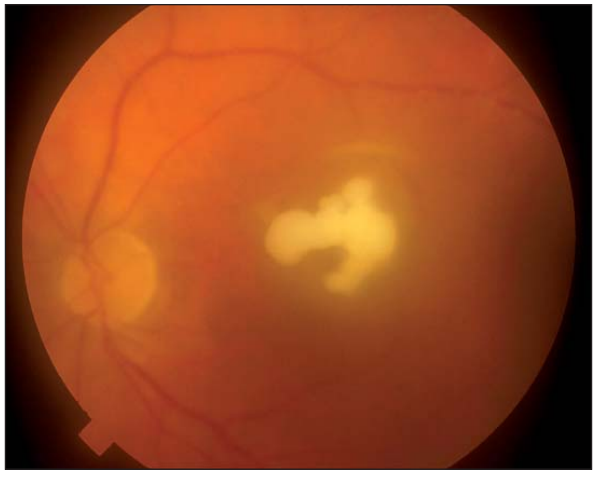
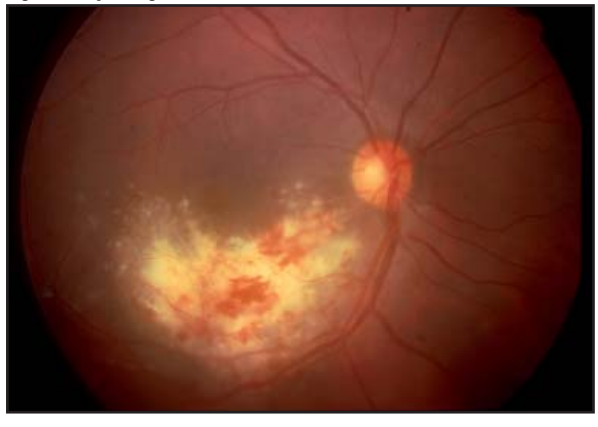


Figure 4. Cytomegalovirus retinitis.



Conclusions

Any septic focus can result in haematogenous spread of infection to the eye. If this occurs, it indicates pronounced septicaemia. Systemic antibiotic use then requires careful review. It is mandatory to seek ophthalmic advice when patients with chronic illness, an immunocompromised status or a nidus of infection present with a red, painful eye or complain of visual symptoms. All patients with candidaemia must be reviewed by an ophthalmologist.

Metastatic endophthalmitis carries a grave prognosis, not only for the eye, but also for the general wellbeing of the patient (Okada et al, 1994). Management of these patients requires a collaborative approach with both physicians and ophthalmologists involved. **BJHM**

Conflict of interest: none.

Albrecht SJ, Fishman NO, Kitchen J et al (2006) Reemergence of gram-negative health care-associated bloodstream infections. *Arch Intern Med* **166:** 1289–94

Biron KK (2006) Antiviral drugs for cytomegalovirus diseases. *Antiviral Research* **71:** 154–63

Breit SM, Hariprasad SM, Mieler WF, Shah GK, Mills MD, Grand MG (2005) Management of endogenous fungal endophthalmitis with voriconazole and caspofungin. *Am J Ophthalmol* **139**(1): 135–40

Brooks RG (1989) Prospective study of Candida endophthalmitis in hospitalized patients with candidaemia. *Arch Intern Med* **149:** 2226–8

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

Coll GE, Lewis H (1994) Metastatic choroidal abscess and choroidal neovascular membrane associated with *Staphylococcus aureus* endocarditis in a heroin user. *Retina* **14:** 256–9

Deayton JR, Griffiths PD (2000) When can cytomegalovirus prophylaxis and maintenance therapy be stopped in HIV disease? *Curr Opin Infect Dis* **13:** 637–41

Feman SS, Nichols JC, Chung SM, Theobald TA (2002) Endophthalmitis in patients with disseminated fungal disease. *Trans Am Ophthalmol Soc* **100:** 67–71

Greenwald MJ, Wohl LG, Sell CH (1986) Metastatic bacterial endophthalmitis: a contemporary reappraisal. *Surv Ophthalamol* **31:** 81–101

Hariprasad SM, Shah GK, Mieler WF et al (2006) Vitreous and aqueous penetration of orally administered moxifoxacin in humans. *Arch Ophthalmol* **124**(2): 178–82

Harris EW, D'amico DJ, Bhisitkul R, Priebe GP, Peterson R (2000) Bacterial subretinal abscess: a case report and review of the literature. *Am J Ophthalmol* **129**(6): 778–85

Holland GL, Shuler JD (1992) Progression rates of cytomegalovirus retinopathy in ganciclovir-treated and untreated patients. *Arch Ophthalmol* **110:** 1435–42

Jackson TL, Eukyn SJ, Graham EM, Stanford MR (2003) Endogenous bacterial endophthalmitis: a 17-year prospective series and review of 267 reported cases. *Surv Ophthalamol* **48:** 403–23

Jacobson MA, Mills J (1988) Serious cytomegalovirus disease in the acquired immunodeficiency syndrome (AIDS). Clinical findings, diagnosis, and treatment. *Ann Intern Med* **108:** 585–94

Kontoyiannis DP, Bodey GP, Mantzoros CS (2001) Fluconazole vs amphotericin B for the management of candidaemia in adults: a meta-analysis. *Mycoses* **44:** 125–35

Koul S, Philipson A, Philipson BT (1989) Incidence of endophthalmitis in Sweden. *Acta Ophthalmologica* **68:** 466–9

Laverdiere M, Hoban D, Restieri C, Habel F (2002) In vitro activity of three new triazoles and one echinocandin against *Candida* bloodstream isolates from cancer patients. *J Antimicrob Chemother* **50:** 119–23

Lazarus HM, Blumer JL, Yanovich SL, Schlamm H, Romero A (2002) Safety and pharmoacokinetics of oral voriconazole in patients at risk of fungal infection: a dose escalation study. *J Clin Pharmacol* **42**(4): 395–402

Lesk MR, Amman H, Marcil G et al (1993) The penetration of oral ciprofloxacin into the aqueous humour, vitreous, and subretinal fluid of humans. *Am J Ophthalmol* **115:** 623–8

Ling R, James B (1998) White-centred retinal haemorrhages (Roth spots). *Postgrad Med J* **74:** 581–2

Lynn WA (2000) Bacteraemia. *J R Coll Physicians Lond* **34:** 536–40

Lynn WA, Lightman S (2004) The eye in systemic infection. *Lancet* **364:** 1439–50

Maxwell DP, Brent BD, Diamond JG, Wu L (1991) Effect of intravitreal dexamethasone on ocular histopathology in a rabbit model of endophthalmitis. *Ophthalmology* **98:** 1370–5

Okada AA, Johnson RP, Liles WC, D'Amico DJ, Baker AS (1994) Endogenous bacterial endophthalmitis. Report of a ten-year retrospective study. *Ophthalmology* **101:** 832–8

Pappas PG, Rex JH, Lee J et al (2003) A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis* **37:** 634–43

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

Power NR, Schein OD, Gieser SC et al (1994) Synthesis of the literature on visual acuity and complications after cataract extraction with intraocular lens implantation. *Arch Ophthalmol* **112:** 239–52

Rex JH, Bennett JE, Sugar AM et al (1994) A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. *N Engl J Med* **331:** 1325–30

Sallam A, Lynn W, McCluskey P, Lightman S (2006) Endogenous Candida endophthalmitis. *Expert Rev Anti Infect Ther* **4:** 675–85

Shorr AF, Chung K, Jackson WL, Waterman PE, Kollef MH (2005) Fluconazole prophylaxis in critically ill surgical patients: a meta-analysis. *Crit Care Med* **33:** 1928–35

Smiddy WE (1998) Treatment outcomes of endogenous fungal endophthalmitis. *Curr Opin Ophthalmol* **9**(3): 66–70

Smith KG, Ihle BU, Heriot WJ, Becker GJ (1995) Metastatic endophthalmitis in dialysis patients. *Am J Nephrol* **15:** 78–81

Takebayashi H, Mizota, A, Tanaa M (2006) Relation between stage of endogenous fungal endophthalmitis and prognosis. *Graefe's Arch Clin Exp Ophthalmol* **244**(7): 816–20

Vincent JL, Bihari DJ, Suter PM et al (1995) The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. *JAMA* **274**(8): 639–44

Wenzel RP, Gennings C (2005) Bloodstream infections due to Candida species in the intensive care unit: identifying especially high-risk patients to determine prevention strategies. *Clin Infect Dis* **41**(Suppl 6): S389–93

Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB (2004) Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* **39:** 309–17

Wright WL, Wenzel RP (1997) Nosocomial Candida Epidemiology, transmission, and prevention. *Infect Dis Clin North Am* **11**(2): 411–25

Wong JS, Chan TK, Lee HM, Chee SP (2000) Endogenous bacterial endophthalmitis. An East Asian experience and a reappraisal of a severe ocular affliction. *Ophthalmology* **107:** 1483–91

KEY POINTS

- Metastatic endophthalmitis is a potentially blinding condition.
- It is the result of haematogenous spread of infecting organisms to the eye from a site of infection elsewhere in the body.
- Metastatic endophthalmitis commonly presents with symptoms of a red, painful eye, often with blurred vision in a generally unwell patient.
- Vigilance is required with patients in an intensive care setting where symptoms may not be reported.
- All patients suspected of having metastatic endophthalmitis and all patients with blood-culture proven candidaemia require urgent referral to an ophthalmologist.