Chapter 12
Endophthalmitis in Newborns and Preverbal Children

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Endophthalmitis in newborns and preverbal children constitutes only a small proportion of all endophthalmitis visiting a hospital. While most principles and practice of evaluation and managing endophthalmitis in this vulnerable group are similar to other cases of endophthalmitis described in this book, important considerations are highlighted in this chapter.

Neonatal and infantile endophthalmitis is mostly from an endogenous source of infection and is the main focus of this chapter. Rarely it could be following post-accidental and non-accidental trauma, post-intraocular surgery, or microbial keratitis especially after keratomalacia, gonococcal keratoconjunctivitis, or congenitally anesthetic cornea. Trauma remains the most important cause in older children followed by post-intraocular surgical infections that are dealt with elsewhere in this book and are mostly similar to adult cases.

Endogenous endophthalmitis in neonates is a rare clinical situation and constitutes 0.1–4% of all endogenous endophthalmitis cases [1, 2]. In the USA, the incidence of endophthalmitis reported from one neonatal intensive care unit (NICU) was 0.14% of all admitted babies [3]. Endogenous endophthalmitis is more common in East Asia and India with large series reported that included the neonates [2, 4].

Clinical Presentations and Common Organisms

Endophthalmitis in newborns presents as two distinct clinical presentations, and a third rare type mostly depending upon the virulence of the causative organisms and treatment given. A fulminant, acute inflammation (Fig. 12.1), which is mostly, though not always, due to virulent gram-negative organisms, is the commonest. The causative organisms include *Pseudomonas*, *Klebsiella*, *E. coli*, *Acinetobacter*, etc.

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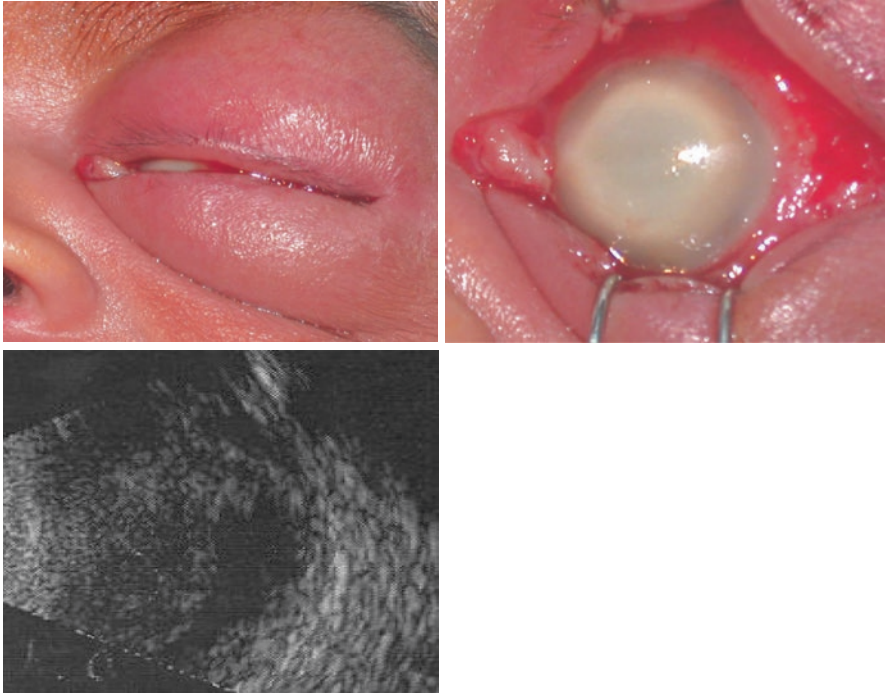e-mail: subhadra@lvpei.org

Fig. 12.1 Fulminant gram-negative neonatal endogenous endophthalmitis. Note periorbital edema (*top left*), conjunctival chemosis, corneal edema, and exudates in anterior chamber (*top right*). Ultrasonography shows vitreous echoes, choroidal thickening, and low reflective retinal detachment (*bottom left*)


Fig. 12.2 Ventriculoperitoneal (VP) shunt induced *Fusarium* endophthalmitis. *Left*—note leucocoria and lens abscess. Aqueous and vitreous tap under topical anaesthesia, followed by intraocular antibiotic injection, was done in this patient

[1–4]. The gram-positive organisms include methicillin-resistant *Staphylococcus aureus* (MRSA), *Bacillus* and *Streptococcus*, and rarely vancomycin-resistant *Staphylococcus epidermidis* (VRSE) [5]. Rare cases with fulminant picture may be of fungal etiology such as *Fusarium* (Fig. 12.2) from a ventriculoperitoneal (VP) shunt [2] or virulent *Herpes simplex* virus (HSV) infections [3].

The second clinical picture is of a very low-grade retinal infiltrate, diagnosed on routine retinal screening. This presents as a single or multiple yellow-white lesions varying from pinhead to few millimeter size, minimally elevated from the retinal surface or as a small subretinal abscess with indistinct borders. The most common causative organism is *Candida albicans and Candida tropicalis* (Fig. 12.3). Vitritis is

Fig. 12.3 Non-fulminant endophthalmitis. Fungal retinitis: *top* and *middle*—presumed *Candida*, early and active phase showing typical retinal infiltrates. *Bottom*—advanced stage with vitreopathy and retinal folds that needs urgent lens-sparing vitrectomy without any subretinal treatment
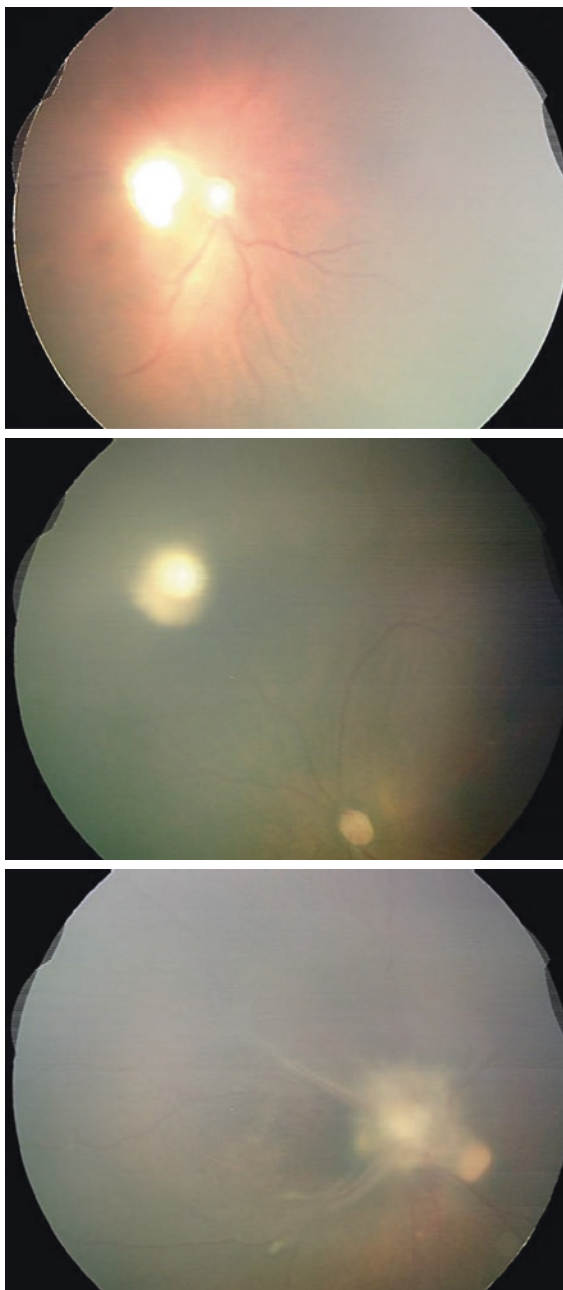
minimal or absent to start with but gradually becomes manifested as the disease progresses. This characteristic clinical diagnosis is sufficient to start antifungals as the lesions are very classic and typical. Low-grade viral retinal infections from HSV and cytomegalovirus (CMV) also start as mild to moderate diffuse retinitis without vitritis (Fig. 12.4) and later can progress to severe vitritis and sometimes keratitis [6].

Fig. 12.4 Viral retinitis (CMV/HSV) always shows some chorioretinal scars in addition to retinitis
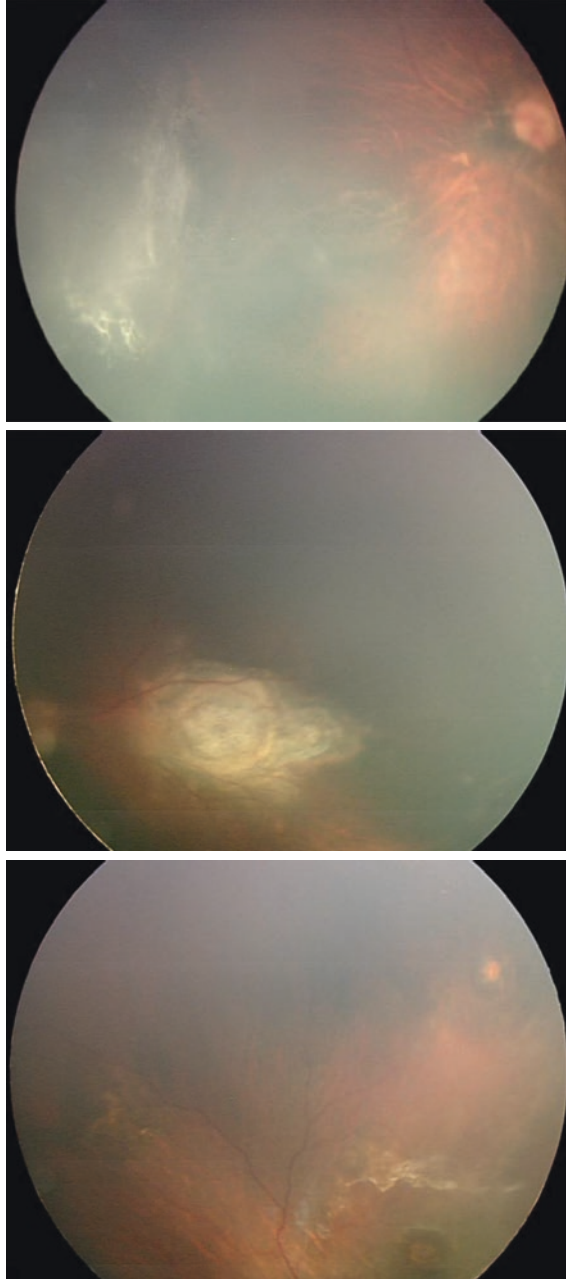
Rarely a third type of clinical picture, partially resolved bacterial endogenous endophthalmitis presents as a less severe infection, after having received parenteral antibiotics during septicemia. These present mostly as a low-grade partly organized subretinal abscess (Fig. 12.5) or vitritis or organized leucocoria (Fig. 12.6) resembling a pseudoglioma due to retinal necrosis and retinal detachment. Another rare clinical presenta-
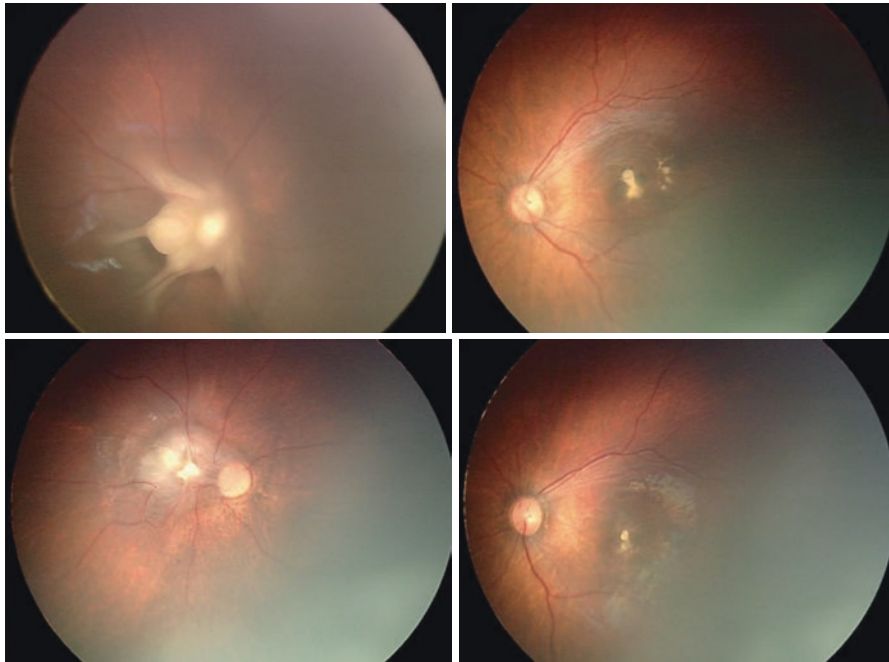

Fig. 12.5 Partially resolved endophthalmitis. Blood culture: *E coli*. *left panel*—preoperative (Top *left*) and post lens-sparing vitrectomy (Bottom *Left*). *Right panel*—Preoperative (Top *Right*) and post-systemic antibiotics (Bottom *right*)
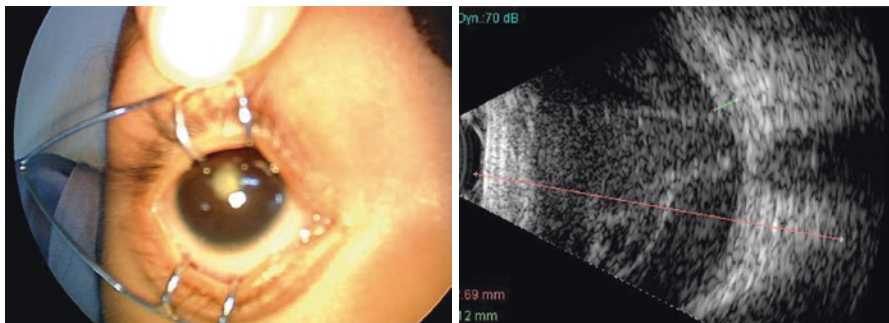

Fig. 12.6 Partially resolved endophthalmitis with systemic antibiotics noted few days after an acute systemic septic episode. This child presented with leucocoria and a shrunken globe resembling a pseudoglioma (*left*). The child was referred as a case of retinoblastoma. The ultrasonography shows no mass but showed a degenerated retinal detachment with low-intensity echoes in vitreous and subretinally—a prephthisical stage (*right*)

tion is a localized anterior chamber granuloma or a very focal iris abscess (authors' experience) that can respond to systemic antimicrobials (anterior endophthalmitis).

Risk factors: Prematurity with low birth weight and hospitalization has been associated in 80% babies presenting with neonatal endophthalmitis [1–4]. Rarely, healthy and normal-weight term babies without any apparent risk factor get such infections [2–4]. The common risk factors are listed in Table 12.1. In the USA, over the years, possibly due to implementation of strict asepsis protocols and attention to the risk factors, there has been a declining incidence of neonatal endogenous endophthalmitis; it reduced from 8.7 per 100,000 babies in 1986 to 4.42 per 100,000 babies in 2006 [7]. In a prospective case series of neonatal candidemia with a prevalence of 1.1 per 100 NICU discharges, endophthalmitis was seen in 2 of 20 babies where eye was evaluated [8].

Diagnostic criteria: Cultures may not be always positive. Hence only laboratory-based confirmation is not adequate to identify all infected endophthalmitis cases, especially of endogenous origin [1–7]. Diagnostic criteria are given in the Table 12.2.

Table 12.1 Susceptibility and risk factors: [1–4, 7]

• Premature and low birth weight (especially less than 1500 g)
• Compromised immune status
• Hospital admission
• Indwelling catheters, infusion pumps, ventilators, implants
• Poor handwashing and hygiene of healthcare workers not practicing good barrier nursing
• Umbilical sepsis
• Bacteremia/candidemia
• Blood transfusion
• Pneumonia/septic abscesses/meningitis
• Cross contamination from other infected babies
• Nursery infection outbreaks such as *Candida, Meningococcus*, etc.

Table 12.2 Diagnostic criteria for neonatal endophthalmitis

Any two of the following five clinical and laboratory features can be considered as a case of neonatal endogenous endophthalmitis:
1. Inflammation of intraocular tissues where except for an infective etiology, no other underlying cause is detected
2. Clinical involvement of retina or vitreous showing typical features of exudation and/or inflammation
3. Any intraocular sample shows significant growth on culture
4. Any of the body tissues/fluid shows significant growth or microbial organisms. Common samples include blood, urine, umbilical cord stump swab, swab from any abscess, etc. in association with ocular inflammation
5. PCR is positive for eubacterial or panfungal or specific viral DNA from ocular sample in presence of ocular inflammation

Investigations

1. All cases suspected to have neonatal and infantile endophthalmitis should have a careful ocular ultrasonography (USG-B) scan with corresponding A-Scan. Endophthalmitis eyes in early stages may have normal USG but in most cases will show low-intensity echoes. USG helps to confirm diagnosis and identifies poor prognostic indicators like retinal detachment, choroidal detachment, membranous echoes (Fig. 12.1, 12.6), and dense echoes filling most of the vitreous cavity. In all cases careful USG including immersion scan should also be done at low gain to evaluate all areas for any mass lesions or calcifications that would suggest an underlying retinoblastoma, which can masquerade as orbital cellulitis or endophthalmitis (Fig. 12.7). If possible, this is done preferably under general anesthesia as sometimes in a crying and struggling child one may miss scanning some areas that contain a hidden underlying tumor. Intraocular cysticercosis that can masquerade as endophthalmitis is also very well diagnosed by USG in most cases. USG is much more sensitive and specific than CT scan or MRI in the diagnosis of neonatal and pediatric endophthalmitis.

2. Find source of infection: Detailed antenatal history must include episodes of fever, septicemia, or vaginal discharge or eruptions in the mother, the mode, and setting of delivery including rural or home deliveries and puerperal sepsis in mother, details of postnatal hospitalization, culture from tubes/ cannulas, etc. for any infective focus like septic arthritis, meningitis, liver abscess, pneumonia, blood cultures, or cultures from urine or other infected body fluids. Evaluation of umbilicus may reveal the source (Fig. 12.8). History should also record any septic epidemic in the nursery at the time of stay of the index case. Thorough systemic evaluation is essential. Past culture and neonatal course reports should be reviewed in consultation with the child healthcare givers.

3. Detailed evaluation of fellow eye including dilated indirect ophthalmoscopy fundus examination at each visit, both in the clinic and whenever the opportunity arises, under general anesthesia additionally, is necessary (Fig. 12.5).

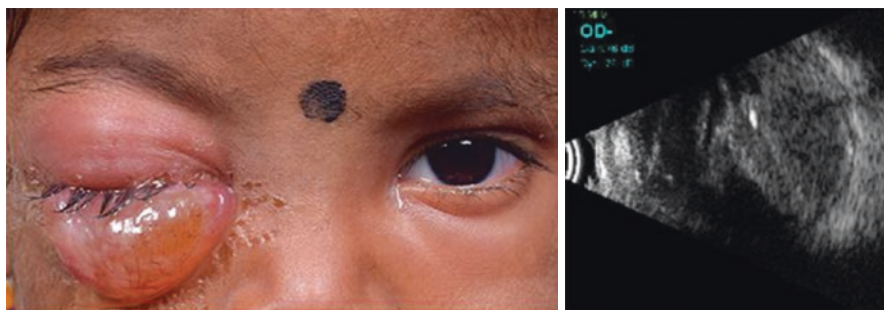

Fig. 12.7 Retinoblastoma can present as orbital cellulitis. *Left*—orbital cellulitis with lid edema, conjunctival chemosis; *right*—USG showing large intravitreal mass with calcification and choroidal thickening. Courtesy: Swathi Kaliki, MD

4. Screen other twin/triplets nursery babies. Examination of mother including vaginal swabs, when indicated, helps.
5. All babies with candidemia/bacteremia need dilated fundoscopy, especially if having prolonged infection for more than 2 weeks.
6. All premature babies also need regular fundoscopy for associated ROP; this will need comanagement.
7. Baby must be co-evaluated for other systemic problems that can be life threatening such as septicemia, meningitis, endocarditis, peritonitis, septic liver abscess, etc.

Fig. 12.8 Newborn showing left eyelids edema (*top*), conjunctival congestion, corneal edema, nearly flat anterior chamber, and leucocoria with lens abscess (*middle*). Umbilical sepsis was a possible source of infection (*Bottom*)
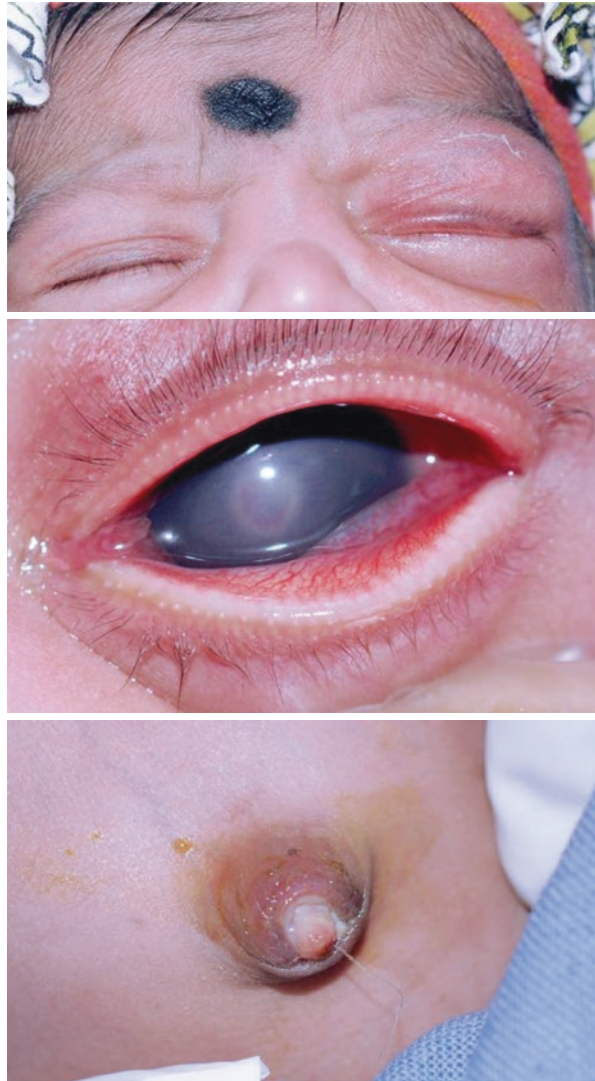
Differential diagnosis: Endogenous endophthalmitis can mimic many other ocular conditions in newborns and small babies. Each of these conditions need attention to clinical, laboratory, imaging, and ancillary testing to arrive to a reasonable diagnosis. Table 12.3 provides other differential diagnosis.

Management: In absence of any large randomized trials or large series of cases of this rare condition, the broad principles of endophthalmitis management are the same in neonates and small children as in adults. These include prompt clinical and microbiological diagnosis and initiation of empirical intravitreal antimicrobials followed by specific modification of antimicrobials based on clinical response and laboratory diagnostic reports. There are however numerous challenges specific to neonatal and infantile endophthalmitis cases (Table 12.4).

Modifications are needed from adult protocols to address some of these challenges. For example, babies who are sick and not fit for general anesthesia could

Table 12.3 Differential diagnosis of endogenous endophthalmitis in neonates and infants

Congenital nasolacrimal duct obstruction
Mucopurulent conjunctivitis including *gonococcal*
Infectious keratitis
Orbital cellulitis
Retinoblastoma
Congenital cataract
Primary hypoplastic primary vitreous (PHPV), other pseudogliomas like retinal dysplasia, etc.
Differential diagnosis in preverbal children beyond infancy:
All above and
trauma, toxocariasis, cysticercosis, and keratomalacia

Table 12.4 Challenges in management of endogenous endophthalmitis in small children [2–4]

• Fragility of child and unfit for general anesthesia
• Systemic co-morbidity especially cardiac (PDA), respiratory (pneumonia), neurological (meningitis/encephalitis), and hematological (anemia, thrombocytopenia)
• Retinal detachment and necrosis preexisting due to fulminant bacteria
• Unilateral aphakia and dense amblyopia following surgery
• Glaucoma/retinal detachment/hypotony after surgery
• Concomitant retinopathy of prematurity (ROP) that can worsen rapidly
• Systemic and ocular cultures may be sterile as patient may already have received systemic antimicrobials or sample may be too small
• Multidrug resistant nosocomial infections
• Logistics of coordination with neonatologists/pediatricians and transportation of babies to ophthalmology operating room that may be remote from the child care facility
• Lack of clinical trial/large series/meta-analysis data. Lack of consensus statements in literature
• Lack of drug dosing information for intravitreal and sometimes for systemic therapy
• No neonatal dose eye drops information or formulations available
• Potential for neonatal drug toxicity, but no literature readily available
• Delayed referral

undergo aqueous/vitreous tap under topical anesthesia with intravitreal antibiotics (and steroids, if so considered) in cases presenting with fulminant endophthalmitis (Fig. 12.2). This provides adequate identification of infecting agent and appropriate antibiotic selection; it also provides control of infection that helps to avoid evisceration even in eyes presenting as panophthalmitis. Since most cases are nosocomial and multidrug resistant, microbiological work-up becomes essential. In fungal retinal infiltrate, only intravitreal amphotericin B is given (half adult dose), and no sample is taken as the anterior vitreous or aqueous will not show any results in this scenario, and treatment is based on the typical clinical picture. If child is fit for general anesthesia, then depending on clinical severity, lens-sparing vitrectomy or vitrectomy with lensectomy is done with sclerotomy at a distance of 1.0 mm from limbus in neonates and infants due to underdevelopment of pars plana in these eyes. In one of the largest published series on neonatal endophthalmitis, all eyes with *Candida* infection could be salvaged by intravitreal amphotericin B under topical anesthesia followed promptly by lens-sparing vitrectomy (Fig. 12.3, 12.5) as soon as vitritis developed [2].

Unlike adults, in neonates, vitreous involvement can lead to rapid folding, stretching, and anterior elevation of the retina (Figs. 12.3 and 12.5). Early surgical intervention can help to flatten these folds before they get elevated far enough to touch the lens, which would necessitate lensectomy. The principles are similar to vitrectomy for ROP-related stage 4A detachments, that progress to require lensectomy if not operated urgently. Once lensectomy is needed, the prognosis becomes poor not only due to challenge of managing a unilateral aphakia and amblyopia at this young age but also due to the high risk of secondary glaucoma [4]. Hence early surgery appears more favorable [2].

Results: Most gram-negative fulminant bacterial cases are reported to resolve with phthisis bulbi or need evisceration. Evisceration can be avoided by managing with intraocular antibiotics and steroids in the eyes that present with fulminant infection [2]. Occasional good outcomes are reported in few cases of fulminant infection, especially those who are diagnosed and managed by immediate surgery. This requires vigilance, high degree of suspicion by treating pediatrician, and a whole lot of coordination to get baby rapidly fit and taken up for surgery [5]. We reported a large series of 31 eyes of 26 babies of neonatal endophthalmitis; in this series all the eyes with suspected *Candida* could be salvaged with good visual outcomes while all the bacterial fulminant eyes became phthisical, but none progressed to evisceration [2]. High mortality from septicemia or meningitis has been reported in some series, and this would depend on the causative organism and clinical situation [8–10]. In a study on long-term outcomes of neonatal *Candida* endophthalmitis treated by systemic therapy alone (intravenous amphotericin B/oral fluconazole), 7 of 11 eyes achieved good outcomes. All three eyes that had poor outcome were due to vitreous traction and macular lesions that did not undergo prompt surgery [11]. In some cases, fungal infections can present as a lens abscess that is possibly a result from hematogenous spread through the persistent tunica vasculosa lentis in premature babies [12]. These eyes have poor outcomes due to inability of systemic drugs to reach the poorly vascularized lens substance as the hyaloid system regresses,

leaving a nidus of infection within the substance of the lens [12]. Prompt lensectomy and intravitreal antifungals would be needed in such cases [12].

Few cases of coexisting ROP in the setting of intraocular infection have been reported. There may be more progression of ROP due to inflammatory cytokines and angiogenic factors [12]. Treatment would also be challenging in view of media haze. Successful management of such cases by surgery or laser has been reported.

Guidelines for surveillance: All babies who are in hospital and diagnosed as having candidemia/bacteremia need regular fundoscopy to detect any ocular spread. This could be weekly in case of candidemia [12] and daily in case of gram-negative septicemia. Any inflammation around eyes (lid edema/erythema, conjunctival injection, ocular discharge) requires pupil dilatation and fundoscopy. The widespread practice of using empirical antibiotic eye drops with a provisional suspicion of a "simple mucopurulent conjunctivitis" without a "red glow" could lead to a delayed diagnosis and loss of a salvageable eye.

Frequently Asked Questions

1. *Should vitrectomy/intravitreal antimicrobials be done early or late in neonatal endophthalmitis when retina is visualized?*
   A: We believe that under topical anesthesia, neonates can receive intravitreal antimicrobials, just like adults, and need not wait for systemic status to improve for general anesthesia fitness. This allows lens-sparing vitrectomy/intravitreal approach early. Delaying treatment could necessitate lensectomy that could progress to unilateral amblyopia and glaucoma.

2. *When, how often and who should do fundoscopy in babies diagnosed to having bacteremia/candidemia in the nursery.*
   A: All babies with systemic infection should undergo mandatory dilated indirect ophthalmoscopy at least weekly in active phases of infection and promptly in case of any redness or sign of ocular inflammation during follow-up.

3. *When, how often and who should do fundoscopy in the nursery in babies who get red eye and /or mucopurulent discharge from the eyes?*
   A: All such babies need a red glow fundus test by physician after dilating pupils with 1% tropicamide on daily rounds. Any suspicion should prompt urgent evaluation by a competent ophthalmologist using indirect ophthalmoscopy.

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