

Intraocular infections in the neonatal intensive care unit

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Background: The purpose of this study was to report on the incidence and treatment outcomes of endogenous endophthalmitis among newborns in the neonatal intensive care unit (NICU) of a single medical center.

Methods: This was a noncomparative, retrospective case series of endogenous endophthalmitis among infants at the Jackson Memorial Hospital NICU treated between March 1, 2002 and March 1, 2007.

Results: Of 4323 infants admitted to the NICU, seven eyes of six (0.139%) infants (two males, four females) were diagnosed with endophthalmitis during the study period. Four patients were born prematurely with a mean gestational age of 27.5 weeks and a mean birth weight of 1153 g. Retinopathy of prematurity was reported in two of the six patients. Mean follow-up was 3.5 years. The diagnosis was confirmed by positive cultures or polymerase chain reaction testing at a median age of 34 postnatal days. Positive cultures included *Candida albicans* (n = 4), *Pseudomonas aeruginosa* (n = 1), and *Herpes simplex* type 2 (n = 1). All patients received systemic treatment and five received adjunctive ophthalmic interventions, including intravitreal antibiotics in five eyes of four patients and vitrectomy with pars plana lensectomy in three eyes. One patient underwent primary enucleation and another had delayed evisceration. In the remaining five eyes, there was a normal appearing posterior segment and normal intraocular pressures at last follow-up.

Conclusion: Endogenous endophthalmitis is a rare complication in infants in the NICU, but may occur in patients with candidemia, bacteremia, retinopathy of prematurity, and low birth weight. Despite early and appropriate treatment, involved eyes may have poor outcomes.

Keywords: endogenous endophthalmitis, neonatal intensive care unit

Introduction

Endogenous endophthalmitis is a rare and visually devastating disease characterized by hematogenous dissemination of micro-organisms from a focus in the body, that in turn cross the blood-brain barrier and inoculate the intraocular tissues. Endogenous endophthalmitis has been well described in adults, but few cases have been reported in the neonatal population.

In a large case series of endophthalmitis occurring in children and young adults, the most common endophthalmitis category was in the setting of trauma.¹ In contrast, endophthalmitis in infants is mostly endogenous and results perinatally from vertical transmission or postnatally from contaminated intravascular catheters, respiratory equipment, or caregivers.²⁻⁶ The most commonly described pathogens in neonatal endophthalmitis are *Candida* species, group B streptococci, *Pseudomonas aeruginosa*, and other Gram negative bacteria.⁷⁻¹¹

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Neonates in the neonatal intensive care unit (NICU) with a diagnosis of septicemia or fungemia are routinely screened to rule out ocular involvement. Risk factors of developing endophthalmitis in neonates include candidemia, bacteremia, retinopathy of prematurity, respiratory disorder, blood transfusion, fetal hemorrhage, and low birth weight.¹²

The mainstay of treatment for endogenous endophthalmitis includes systemic antimicrobials with adjuvant intravitreal injections and pars plana vitrectomy in selected patients. In general, the visual prognosis is unfavorable, and the mortality rate is associated with virulence of the organisms causing underlying neonatal septicemia. Visual outcomes are generally more favorable among those surviving candidemia when compared with bacterial septicemia.^{13–17}

Materials and methods

A retrospective review of the medical records was conducted for all patients admitted to the NICU at Jackson Memorial Hospital between March 1, 2002 and March 1, 2007. This study was approved by the internal review boards at the University of Miami Miller School of Medicine and Jackson Memorial Hospital, and all procedures were performed in accordance with the 1951 Declaration of Helsinki.¹⁸

The neonatology division of Jackson Memorial Hospital maintains a clinical database of all newborns admitted to the NICU. A pediatric retina specialist (AMB) conducted a dilated examination of the fundus when blood, urine, wound, or cerebrospinal fluid cultures confirmed systemic infection or as screening for retinopathy of prematurity. Indirect ophthalmoscopy with or without scleral depression was performed one hour after pupillary dilation. No infant was too ill to undergo complete ophthalmoscopic examination.

Neonatal patients with endophthalmitis were identified clinically by anterior segment findings and by the presence of characteristic vitreous opacities or chorioretinal infiltrates. Septicemia was confirmed in conjunction with the neonatologists by clinical signs of sepsis and positive blood, urine, cerebrospinal fluid, vitreous, or wound cultures, or polymerase chain reaction. Broad-spectrum antibiotics (ampicillin and gentamicin) and/or antifungals (fluconazole or amphotericin) were initiated when sepsis was suspected, and intravascular catheters were changed if blood cultures were positive. Intravitreal antibiotics and/or antifungals and vitreous surgery were performed when the initial clinical signs were severe or the vitritis worsened despite systemic treatment.

Results

Of 4323 infants admitted to the NICU at Jackson Memorial Hospital during the 5-year study period, seven eyes of six infants (two males, four females) had endophthalmitis. Mean follow-up was 3.5 years. Four infants were transferred from an outside NICU for worsening systemic and ocular complications. Four patients were born prematurely with a mean gestational age of 27.5 weeks and a mean birth weight of 1153 g (three patients weighed ≤ 1000 g).

The four preterm infants had multiple comorbidities associated with prematurity, including bronchopulmonary dysplasia, hydrocephalus, intraventricular hemorrhage, anemia, rickets, and hypothyroidism. Each was screened for development of retinopathy of prematurity, which was found in two patients and required treatment. Two patients had tunica vasculosa lentis.

All six infants showed constitutional signs of infection, including fever, poor feeding, lethargy, worsening respiratory status, or bradycardia. Ophthalmologic consultation was sought immediately in five of six infants, and in these cases, the ophthalmologist used indirect ophthalmoscopy to confirm the diagnosis on the same day. The one infant with delayed consultation was constitutionally improving after three weeks of liposomal amphotericin B, and ophthalmology consultation was sought only after corneal edema and leukocoria was noted in the right eye.

The mean number of postnatal days to time of positive culture was 34 (range 21–43). Cultures or polymerase chain reaction identified the pathogens in all cases. Although all patients were tested, only two patients had positive blood and urine cultures. Diagnostic extraocular cultures were obtained invasively from multiple sites in three patients, two from hepatic abscesses, and one from pleural fluid. Anterior chamber polymerase chain reaction was positive in one patient. Ocular cultures were obtained in five patients, four from vitreous cultures, and two from removed ocular contents (enucleation and evisceration specimens). Cultures grew from multiple sites in four patients. *Candida albicans* was the causative organism

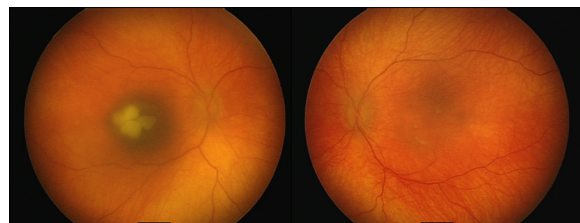


Figure 1 Fundus images of the right and left eyes of patient 4 with bilateral well circumscribed chorioretinal lesions in the macula. The lesion is more prominent in the right eye.

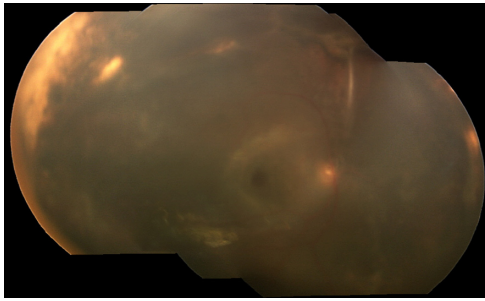


Figure 2 Montage image of the fundus of patient 6 showing diffuse necrotizing retinitis and vitritis.

in four patients (Figure 1). *Pseudomonas aeruginosa* and herpes simplex virus type 2 each caused endophthalmitis in one patient (Figure 2). All cases of *C. albicans* were sensitive to fluconazole, and the case of *P. aeruginosa* was sensitive to

piperacillin and third-generation cephalosporins. Treatment and outcomes are summarized in Table 1.

Because long-term follow-up was not possible in all patients, visual acuity data cannot be presented. Of the seven eyes, two had very poor outcomes (one enucleation (Figure 3) and one evisceration). Other patients recovered with a normal-appearing posterior segment and no sign of recurrent infection.

Discussion

Although colonization of skin and respiratory passages and contamination of indwelling lines and catheters are common events in the NICU, endophthalmitis is a rare complication. Most cases are caused by endogenous pathogens transmitted perinatally or during extended postnatal hospitalization.

Table 1 Clinical features in neonates with endophthalmitis in the neonatal intensive care unit

Patient number/ gender	Age of birth (gestational week)/ birth weight (g)	Etiology	Systemic treatment	Intravitreal injection	Interventional treatment	Other ophthalmic findings
1 (OD)/male	26 weeks/825 g	<i>Candida albicans</i>	Intravenous amphotericin B and fluconazole	Amphotericin B	Pars plana vitrectomy/pars plana lensectomy with removal of pupillary membrane	Glaucoma* in right eye with Baerveldt tube implant
2 (OD)/female	25 weeks/870 g	<i>Candida albicans</i>	Intravenous amphotericin B and fluconazole	Amphotericin B	Pars plana vitrectomy/pars plana lensectomy	Glaucoma* in the right eye with Baerveldt tube implant ROP in both eyes treated with laser ablative therapy
3 (OS)/female	37 weeks/3340 g	<i>Candida albicans</i>	Intravenous fluconazole	Amphotericin B	Enucleation	Glaucoma* in left eye (medically treated with acetazolamide) ROP in right eye treated with laser ablative treatment
4 (OD)/male	40 weeks/3225 g	<i>Candida albicans</i>	Intravenous amphotericin B, fluorocytosine, and fluconazole	Amphotericin B Voriconazole	Pars plana vitrectomy/pars plana lensectomy	
4 (OS)/male	40 weeks/3325 g	<i>Candida albicans</i>	Intravenous amphotericin B, fluorocytosine, and fluconazole	Amphotericin B		
5 (OD)/male	27 weeks/1000 g	<i>Pseudomonas aeruginosa</i>	Intravenous piperacillin, ceftazidime, and gentamicin		Evisceration	ROP
6 (OD)/female	32 weeks/1910 g	<i>Herpes simplex virus</i>	Intravenous aciclovir			

Notes: *Glaucoma developed in patient 1 at age 2 years, in patient 2 at 3 months of age, and patient 3 was referred from an outside institution at 2 months of age with a diagnosis of congenital glaucoma.

Abbreviation: ROP, retinopathy of prematurity.

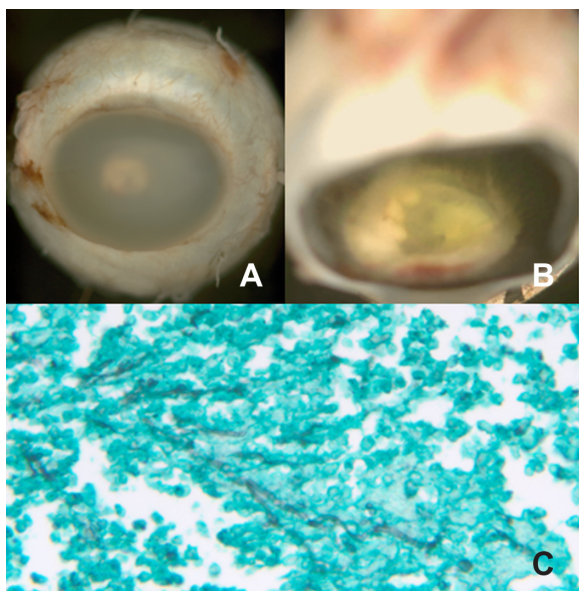


Figure 3 (A) Gross image of the enucleated left eye of patient 3. (B) Gross image of the left eye with the superior cap removed; a retrocorneal tan white material with an admixture of hemorrhage is identified. (C) Histologic section of the left eye (Gomori methenamine silver 20x) showing fungal infiltrate.

Historically, rates of endophthalmitis from septicemia approached 50%.¹⁹ These rates have been dropping over the last three decades from a reported incidence of 8.71 per 100,000 of live births per year in 1998 to only 4.42 per 100,000 in 2006.¹² Improvements in recognition and earlier empiric use of broad-spectrum antibiotics and antifungals for septicemia have possibly reduced the rate of neonatal endophthalmitis to infants whose infection was not successfully controlled with intravenous therapies alone. Thus, in contrast with previously reported series, this cohort of patients required invasive vitreoretinal interventions for successful treatment of infection.

Infants in a NICU are at highest risk for septicemia and endophthalmitis. The presence of tunica vasculosa lentis may be an additional predisposing factor for endophthalmitis in very premature infants with septicemia. Infants with retinopathy of prematurity have increased vascular permeability because of upregulated vascular endothelial growth factor that may allow ocular seeding of septic emboli. Conversely, some authors have demonstrated an association between candidemia and progression to threshold retinopathy of prematurity.^{20,21}

The severity of endophthalmitis presentation in the current study may reflect timing of diagnosis relative to the onset of disease, the virulence of the causative pathogen, or a greater inoculum evading immune constraints. Examinations are routinely performed on premature and very low birth weight infants for retinopathy of prematurity.²² In addition,

early ophthalmologic consultation is advisable in those infants with constitutional symptoms of septicemia or ocular signs, such as corneal edema or leukocoria.

In a study from our institution of endogenous fungal endophthalmitis in adults, 65 eyes of 51 patients were treated. Visual outcomes were poor, especially when the endophthalmitis was caused by mold.²³ Similar to the adult population, the visual prognosis of neonatal endogenous endophthalmitis is often poor, even with early identification and prompt intervention.

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References

1. Thordson JE, Harris L, Hubbard GB III. Pediatric endophthalmitis: a 10-year consecutive series. *Retina*. 2008;28:S3–S7.
2. Saiman L, Ludington E, Pfaller M, et al. Risk factors for candidemia in NICU patients. *Pediatr Infect Dis J*. 2000;19:319–324.
3. Saiman L, Ludington E, Dawson J, et al. Risk factors for candidemia species colonization of neonatal intensive care unit patients. *Pediatr Infect Dis J*. 2001;20:1119–1124.
4. Lopez-Sastre JB, Gil D, Coto-Coballo MD, et al. Neonatal invasive candidiasis: a prospective multicenter study of 118 cases. *Am J Perinatol*. 2003;20:153–163.
5. Leibovitz E, Iuster-Reicher A, Amitai M, Mogilner B. Systemic candidal infections associated with use of peripheral venous catheters in neonates: a 9-year experience. *Clin Infect Dis*. 1992;14:485–491.
6. Yancey MK, Duff P, Kubilis P, Clark P, Frentzen BH. Risk factors for neonatal sepsis. *Obstet Gynecol*. 1996;87:188–194.
7. Sparks JR, Recchia FM, Weitkamp JH. Endogenous group B streptococcal endophthalmitis in a preterm infant. *J Perinatol*. 2007;27:392–394.
8. Ness T, Pelz K, Hansen LL. Endogenous endophthalmitis: microorganisms, disposition and prognosis. *Acta Ophthalmol Scand*. 2007;85: 852–856.
9. Wu Z, Uzcategui N, Chung M, Song J, Lim JI. Group B streptococcal endogenous endophthalmitis in a neonate. *Retina*. 2006;26:472–473.

10. Wasserman BN, Sondhi N, Carr BL. Pseudomonas-induced bilateral endophthalmitis with corneal perforation in a neonate. *JAAPOS*. 1999; 3:183–184.
11. Friedlander SM, Raphaelian PV, Granet DB, Goldbaum MH. Bilateral endogenous *Escherichia coli* endophthalmitis in a neonate with meningitis. *Retina*. 1996;16:341–342.
12. Moshfeghi AA, Charalel RA, Hernandez-Boussard T, Morton JM, Moshfeghi DM. Declining incidence of neonatal endophthalmitis in the United States. *Am J Ophthalmol*. 2011;151:59–65.
13. Baley JE, Annable WL, Kliegman RM. Candida endophthalmitis in the premature infant. *J Pediatr*. 1981;98:458–461.
14. Fisher RG, Karlowicz MG, Lall-Trail J. Very low prevalence of endophthalmitis in very low birthweight infants who survive candidemia. *J Perinatol*. 2005;25:408–411.
15. Parke DW II, Jones DB, Gentry LO. Endogenous endophthalmitis among patients with candidemia. *Ophthalmology*. 1982;89:789–796.
16. Brooks RG. Prospective study of Candida endophthalmitis in hospitalized patients with candidemia. *Arch Intern Med*. 1989;149:2226–2228.
17. Chapman RL, Faix RG. Persistently positive cultures and outcome in invasive neonatal candidiasis. *Pediatr Infect Dis J*. 2000;19:822–827.
18. World Medical Organization. Declaration of Helsinki. *BMJ*. 1996;313: 1448–1449.
19. Filice G, Yu B, Armstrong D. Immunodiffusion and agglutination tests for Candida in patients with neoplastic disease: inconsistent correlation of results with invasive infections. *J Infect Dis*. 1997;135: 349–357.
20. Noyola DE, Bohra L, Paysse EA, Fernandez M, Coats DK. Association of candidemia and retinopathy of prematurity in very low birthweight infants. *Ophthalmology*. 2002;109:80–84.
21. Haroon Parupia MF, Dhanireddy R. Association of postnatal dexamethasone use and fungal sepsis in the development of severe retinopathy of prematurity and progression to laser therapy in extremely low-birth-weight infants. *J Perinatol*. 2001;21:242–247.
22. Karlowicz MG, Giannone PJ, Pestian J, Morrow AL, Shults J. Does candidemia predict threshold retinopathy of prematurity in extremely low birth weight (≤ 1000 g) neonates? *Pediatrics*. 2000;105: 1036–1040.
23. Lingappan A, Wykoff CC, Albini TA, et al. Endogenous fungal endophthalmitis: causative organisms, management strategies, and visual acuity outcomes. *Am J Ophthalmol*. 2012;153:162–166.

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