Neonatal Endogenous Endophthalmitis: A Report of Six Cases

abstract

Endogenous endophthalmitis is a rare but potentially blinding complication of neonatal sepsis. Early diagnosis and aggressive treatment are essential to avoid vision loss. Therapeutic options include systemic and intravitreal antibiotics, as well as vitrectomy in selected cases. We report a series of 6 premature very low birth weight neonates who developed endogenous endophthalmitis in our NICU over the past 3 years. Endophthalmitis was part of early-onset sepsis in 2 newborns, both of whom died, and late-onset sepsis in 4 newborns, of which 1 infant died. None of the neonates had any history of previous trauma or intervention to the eye. Maternal screening for congenital infections, including HIV, was negative in all. Causative organisms included Klebsiella pneumoniae (2 cases), Pseudomonas aeruginosa (2 cases), Methicillin-resistant Staphylococcus aureus (1 case), and Candida albicans (1 case). All bacterial isolates showed resistance to first-line antibiotics. Of the 3 survivors, 2 infants had normal vision in the affected eye, and 1 developed phthisis bulbi after corneal perforation and required enucleation. This report draws attention to the emergence of endophthalmitis as a complication of neonatal sepsis in places where, although survival of very low birth weight newborns has increased significantly due to improved care, the burden of infection continues to be high. We emphasize the importance of daily examination of eyes as a part of routine clinical care in septic newborns for early diagnosis of endophthalmitis and prompt intervention in consultation with an ophthalmologist to optimize the outcome.

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KEY WORDS
Candida albicans, endogenous endophthalmitis, premature, newborn, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus

ABBREVIATIONS
IVI—intravitreal injection
MRSA—methicillin-resistant Staphylococcus aureus
ROP—retinopathy of prematurity

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Endophthalmitis is defined as suppurrative inflammation of the internal structures of the eye. It is usually caused by infection, but noninfectious (sterile) endophthalmitis may also occur as an infrequent complication of intravitreal injections. Endophthalmitis of infective origin may be endogenous or exogenous in nature. Endogenous endophthalmitis arises from the seeding of microorganisms into the eye from a distant infection site. Exogenous endophthalmitis results from direct inoculation of microorganisms from outside as a complication of intraocular surgery, retained intraocular foreign bodies, or penetrating ocular trauma. Endogenous endophthalmitis is relatively rare, accounting for only 2% to 8% of all endophthalmitis cases. It occurs most often in immunocompromised individuals and is associated with a poor visual prognosis. Retina, choroid, and the ciliary body are the primary sites of infection within the eye because of their higher blood flow.

Neonatal endophthalmitis is a potentially blinding complication of neonatal sepsis, and management must take into account the unique challenges posed by the anatomic and physiologic constraints of the newborn eye. Although neonatal sepsis is the most common cause of neonatal mortality in India, endophthalmitis is rarely reported. In this communication, we describe 6 cases of endogenous endophthalmitis from our NICU during the past 3 years.

**PATIENT PRESENTATION**

This study was carried out in Sir Sundar Lal Hospital, Banaras Hindu University, Varanasi, India, a tertiary-care hospital catering to high-risk pregnancies in the region. Out of 5968 live-born deliveries over 3 years, 6 babies developed endogenous endophthalmitis, giving an incidence of ~1 case per 1000 live births. Details of the cases are summarized in Table 1. None of the affected neonates had trauma or intervention to the eye before the development of endophthalmitis. Maternal screening for intrauterine infections such as toxoplasma, rubella, cytomegalovirus, herpes, syphilis, and HIV was negative in all patients. Endophthalmitis was part of early-onset sepsis (≤72 hours of age) in 2 and of late-onset sepsis (≥72 hours of age) in 4 patients. Blood culture grew *Klebsiella pneumoniae* (n = 2; 33.3%), *Pseudomonas aeruginosa* (n = 2; 33.3%), *methicillin-resistant Staphylococcus aureus (MRSA)* (n = 1; 16.7%), and *Candida albicans* (n = 1; 16.7%). Ocular ultrasonography (B scan) documented vitreal infiltrates suggestive of endophthalmitis in all the affected cases. Vitreal aspiration revealed thick viscous whitish-yellow purulent material in 4 infants (antemortem in cases 1, 2, and 6, postmortem in case 5). In all cases, vitreal aspirate culture grew the same organism as was found in blood culture. Cases 5 and 6 had spontaneous perforation of the cornea.

After the diagnosis of endophthalmitis was established, we treated these patients with piperacillin-tazobactam and meropenem except case 3, who received cloxacillin and amikacin along with piperacillin-tazobactam, and case 6, who additionally received amphotericin B. Both *Klebsiella* (cases 1 and 2) and *Pseudomonas* (cases 3 and 4) were sensitive to piperacillin-tazobactam and meropenem; MRSA (case 5) was sensitive to vancomycin and tigecycline. In this case, antibiotics could not be changed because the report was available only postmortem. Intravitreal instillation of vancomycin and amikacin was done in cases 1 and 2. Vitrectomy was done in case 6. Infants also received supportive measures such as mechanical ventilation, surfactant therapy, total parenteral nutrition, vasopressor support, phototherapy, and blood component therapy, if needed. Three infants died (cases 1, 2, and 5), and 3 survived (cases 3, 4, and 6). Case 6 developed phthisis bulbi after corneal perforation, which required enucleation. Two infants survived with unimpaired vision in the affected eye (cases 3 and 4).

The visual function of the survivors was assessed at 3- and 6-month follow-up by an ophthalmologist, who looked for normal spontaneous ocular motility, horizontal tracking, color-stimulus tracking, and ocular fixation. Development of social smile in an age-appropriate manner in these infants was also reassuring with regard to vision. None of the infants developed strabismus.

**DISCUSSION**

Endogenous endophthalmitis is a rare complication of neonatal sepsis. Although there are occasional case reports of neonatal endophthalmitis from India, overall incidence is not available. In this series, we observed 1 case of endophthalmitis per 1000 live births. This is in contrast to data from the United States, where the incidence of neonatal endophthalmitis is low and has decreased at a rate of 6% per year between 1998 (8.71 cases per 100 000 live births) and 2006 (4.42 cases per 100 000 live births). The possible reasons for the high incidence of endophthalmitis in our institution may be the burgeoning NICU population of more immunocompromised, extremely low birth weight infants resulting from improved neonatal care, as well as the high rates of infection by antibiotic-resistant microbes, which makes neonatal sepsis difficult to treat and more likely to metastasize.

Risk factors of neonatal endophthalmitis include systemic bacteremia, Candidemia, very low birth weight, and retinopathy of prematurity (ROP). All the neonates in our series were premature, very low birth weight, sick, and had associated comorbidities, as noted in Table 1. The majority of our cases...
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3*</th>
<th>Case 4*</th>
<th>Case 5</th>
<th>Case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk)</td>
<td>26</td>
<td>33</td>
<td>32</td>
<td>28</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Birth wt (g)</td>
<td>833</td>
<td>795</td>
<td>1440</td>
<td>1120</td>
<td>950</td>
<td>1025</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Diagnosis at admission</td>
<td>RDS</td>
<td>Intrauterine pneumonia</td>
<td>Late-onset sepsis</td>
<td>RDS</td>
<td>Intrauterine pneumonia</td>
<td>Late-onset sepsis</td>
</tr>
<tr>
<td>Onset of endophthalmitis</td>
<td>Day 10</td>
<td>30 h</td>
<td>Day 5</td>
<td>Day 4</td>
<td>Day 10</td>
<td>Day 10</td>
</tr>
<tr>
<td>Eye involvement</td>
<td>Right</td>
<td>Both</td>
<td>Right</td>
<td>Both</td>
<td>Both</td>
<td>Left</td>
</tr>
<tr>
<td>Nature of ocular lesion</td>
<td>Ring-shaped corneal opacity (Fig. 1)</td>
<td>Both corneal haziness with loss of red reflex</td>
<td>Both corneal haziness with loss of red reflex</td>
<td>Both corneal haziness with loss of red eye reflex</td>
<td>Both leukocoria in right eye with loss of red reflex and hypopyon in left eye (Fig. 2)</td>
<td>Left totally opaque left cornea with hypopyon (Fig. 3)</td>
</tr>
<tr>
<td>Antibiotics given</td>
<td>Pip-tz+ meropenem</td>
<td>Pip-tz+ meropenem</td>
<td>Cloxacillin+ pip-tz+ amikacin</td>
<td>Pip-tz+ meropenem</td>
<td>Pip-tz+ meropenem</td>
<td>Pip-tz+ meropenem+ amphotericin B</td>
</tr>
<tr>
<td>Intravitreal instillation of vancomycin, amikacin</td>
<td>Given</td>
<td>Given</td>
<td>Not attempted</td>
<td>Not attempted</td>
<td>Not attempted</td>
<td>Vitrectomy done</td>
</tr>
<tr>
<td>Vitreal aspirate</td>
<td>Thick viscous whitish-yellow purulent material</td>
<td>Thick viscous whitish-yellow purulent material</td>
<td>Not consented</td>
<td>Not consented</td>
<td>Thick viscous whitish-yellow purulent material (done postmortem)</td>
<td>Thick viscous whitish-yellow purulent material</td>
</tr>
<tr>
<td>Blood culture</td>
<td>Klebsiella pneumonia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Klebsiella pneumonia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pseudomonas aeruginosa</td>
<td>Pseudomonas aeruginosa</td>
<td>Pseudomonas aeruginosa</td>
<td>MRSA&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Type of sepsis</td>
<td>Late onset</td>
<td>Early onset</td>
<td>Late onset</td>
<td>Late onset</td>
<td>Early onset</td>
<td>Late onset</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>4 d</td>
<td>3 d</td>
<td>—</td>
<td>3 d</td>
<td>5 d</td>
<td>—</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td>Meningitis, shock, DIC</td>
<td>Shock, IVH, ARF</td>
<td>Abscess over xiphisternum</td>
<td>Hyperbilirubinemia, shock</td>
<td>Shock, IVH, PDA, ARF</td>
<td>Shock</td>
</tr>
<tr>
<td>Outcome</td>
<td>Expired on postnatal day 14</td>
<td>Expired on postnatal day 6</td>
<td>Discharged at 3 wk of age</td>
<td>Discharged on request at day 17 of age</td>
<td>Expired on postnatal day 5</td>
<td>Discharged at day 30 of age</td>
</tr>
<tr>
<td>Ophthalmic outcome</td>
<td>—</td>
<td>—</td>
<td>Vision preserved</td>
<td>Vision preserved</td>
<td>—</td>
<td>Left cornea perforated, developed phthisis bulbi</td>
</tr>
</tbody>
</table>

ARF, acute renal failure; DIC, disseminated intravascular coagulation; IVH, intraventricular hemorrhage; pip-tz, piperacillin-tazobactam; RDS, respiratory distress syndrome.

* Diagnosis was presumptive in the absence of vitreal aspiration.

<sup>b</sup> Vitreal aspirate also grew same organism as blood culture.
(4; 66.7%) were part of late-onset sepsis, but in 2 cases, endophthalmitis developed early (30 hours in case 2 and 70 hours in case 5). Such early presentation is unusual, rarely reported in literature, and suggestive of transplacentally acquired infection from the mother. None of the infants in our series had ocular trauma or intervention. This indicates that ocular involvement occurred due to seeding of bacteria from blood-stream infection in these cases. Three of our cases had bilateral ocular involvement; the right eye alone was involved in 2 cases, and the left eye alone in 1 case. As previous reports have shown, in unilateral cases of endogenous endophthalmitis, the right eye is twice as likely to become infected as the left eye, probably because of its greater proximity to direct arterial blood flow. In cases 3 and 4, we suspected endophthalmitis because of corneal haze, loss of red reflex, vitreal infiltrates on ultrasonography B scan, and positive blood culture. However, in the absence of vitreal aspiration, the diagnosis of Pseudomonas endophthalmitis in these cases remains presumptive rather than definitive because parents refused consent for the procedure. The outcome was good in these cases because of the timely initiation of piperacillin-tazobactam and meropenem, and the organisms were sensitive to these antibiotics. Extreme preterm newborns may occasionally have slight corneal haze, which should not be confused with endophthalmitis. Eyes should be examined for any abnormality during the first routine examination after birth.

Because endogenous endophthalmitis is a complication of neonatal sepsis, the causative organisms of endophthalmitis reflect the microbial spectrum of neonatal sepsis. Bacteria causing neonatal endophthalmitis include Pseudomonas spp, Candida albicans, group B Streptococci, Klebsiella spp, Serratia marcescens, and Neisseria meningitidis. In India and other developing countries, Gram-negative bacteria are the most frequent cause of neonatal sepsis whereas Gram-positive organisms are commonly isolated from developed countries. In the present series, Gram-negative organisms were isolated in 4 of 6 (66%) cases. We found Pseudomonas aeruginosa as an offending pathogen in 2 of 6 (33.3%) cases of endophthalmitis, whereas other authors have reported P aeruginosa in 75% cases of invasive neonatal eye infections. The course of pseudomonal endophthalmitis is typically fulminant, developing over hours even with early diagnosis. For survivors, the usual result is blindness of the affected eye. Surprisingly, both of our cases of Pseudomonas endophthalmitis survived with intact vision. Klebsiella pneumoniae was isolated in 2 of our cases, which is rarely reported in neonates. Li et al reported a case of presumed endogenous endophthalmitis by Klebsiella in a premature infant. MRSA was isolated in 1 patient who presented with leukocoria. To our knowledge, endogenous endophthalmitis by MRSA has not been reported in premature neonates, although it has been reported in adults. In the present series, Candida was isolated in 1 patient, who developed hypopyon. Several reports of endogenous endophthalmitis in premature neonates are available with candidiasis with associated cataract formation and ROP. A high index of suspicion is required in making the diagnosis of endophthalmitis. In a critically sick newborn, the attending physician often remains preoccupied with monitoring and support of other vital organs and may overlook eye examination. The importance of regular eye examination in early identification of endophthalmitis in septic newborns cannot be overemphasized. As an initial screening procedure, loss of red reflex should be...
regarded as an early sign, followed by haziness or opacity of the cornea.\textsuperscript{14} Intravitreal tap with culture may confirm endogenous endophthalmitis.\textsuperscript{14} All of our patients developed endophthalmitis within the first 10 days of life. Although regular ROP screening is a part of routine care in many neonatal centers today, it may miss most cases of endophthalmitis because first ROP screening is not done before 3 to 4 weeks of age.

Treatment options include systemic and intravitreal administration of antibiotics and vitrectomy. Parenteral antibiotics are a mainstay of therapy in controlling infection in neonatal endophthalmitis, but other strategies are still controversial. Physiologic handicaps in newborns, particularly the immunocompromised state of premature babies, make them more vulnerable to rapid spread of infection. Under normal conditions, the blood-ocular barrier facilitates maintenance of a sterile environment in the interior of the eye, but it also prevents the elimination of infection by immune mechanisms and restricts entry of systemically administered antibiotics.\textsuperscript{22} The blood-ocular barrier is usually broken down during endophthalmitis, permitting entry of systemic administered antibiotics into the eye. Intravitreal injection (IVI) of antibiotics (a combination of vancomycin with ceftazidime or amikacin) is the mainstay of treatment of endophthalmitis in exogenous postoperative endophthalmitis.\textsuperscript{22} Several authors are of the opinion that the combination of intravitreal vancomycin (1 mg/0.1 mL) and ceftazidime (2.25 mg/0.1 mL) is a better combination compared with vancomycin and amikacin (0.4 mg/0.1 mL).\textsuperscript{23,24} Others have expressed concern that ceftazidime precipitates in vitreous at body temperature, and, because of precipitation, the concentration of free ceftazidime in vitreous may not be sufficiently high for anti-bacterial activity against most common organisms.\textsuperscript{25} The advantage of the IVI technique is the ability to maximize intraocular levels of antibiotics and to avoid the toxicities associated with systemic treatment.\textsuperscript{22} Although IVI circumvents the tight junctions of the blood-ocular barrier, it also carries the risk of vitreous or subretinal hemorrhage, retinal toxicity, retinal detachment, central artery occlusion, uveitis, or lens opacification.\textsuperscript{26}

In severe cases of endophthalmitis in adults, vitrectomy is often used to debride the vitreous cavity of bacteria, inflammatory cells, and other toxic debris and to promote better diffusion of antibiotics and removal of inflammatory membranes.\textsuperscript{3} In 1995, the Endophthalmitis Vitrectomy Study Group demonstrated that vitrectomy may lead to better structural recovery in the eye in certain cases.\textsuperscript{27} Aggressive therapy with vitrectomy and intravitreal antibiotics may result in favorable anatomic outcomes and preservation of the infected eye.\textsuperscript{18,19} Vitrectomy in children, especially neonates, is difficult because of their different anatomy and is a great challenge to ophthalmologists. It is only attempted, with guarded prognosis, in the most severe cases. Common postoperative complications include retinal detachment, disc dragging, cataract, glaucoma, persistent vitreous hemorrhage, and posterior synechia.\textsuperscript{5,28,29} The critical factor for clinicians to assess is whether the potential for significant vision loss from infection outweighs the minimal risk of complications from intravitreal injection of antibiotics that would otherwise quickly sterile the eye. Close coordination between the neonatologist and ophthalmologist skilled in handling sick premature infants is necessary for the management of neonatal endophthalmitis.

The prognosis of endophthalmitis with regard to survival is similar to sepsis. The mortality rate was 50% in our series, and the ophthalmologic prognosis of survivors is poor.\textsuperscript{4} Vision was saved in 2 of our patients, but they require regular follow-up for detection of complications. In view of high mortality and vision loss, early detection of neonatal endophthalmitis in the NICU should be a priority, paying close attention to neonates’ eyes during daily rounds and initiating aggressive management to optimize outcomes.

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