Introduction

Metastatic Endophthalmitis is a potentially devastating albeit rare intraocular infection defined as inflammation of the anterior or posterior segment or both, with involvement of the adjacent ocular wall or as, an inflammatory reaction occurring as a result of intraocular colonization by bacteria, fungi, or rarely parasites [ESCRS]1.

Endophthalmitis can result from exogenous spread after intraocular surgery or trauma, or from adjacent structures. A less common form called endogenous endophthalmitis occurs due to hematogenous spread from a remote infectious site to the eye, resulting in intraocular colonization with inflammation, and subsequent severe loss of vision.

The incidence of endogenous endophthalmitis world wide is estimated to be 2 – 5 % of all cases of endophthalmitis1. Though the pathogen may vary between different geographic areas, the most common bacterial organism is staphylococcus aureus, and the most common fungal organism is candida3.

Predisposing factors for endogenous endophthalmitis, ranges from chronic immune compromising illnesses[renal failure, diabetes mellitus] immunosuppressive diseases and treatment [post organ transplant, human immunodeficiency virus infection, long term intravenous catheters],recent invasive surgeries, gastrointestinal procedures, hepatobiliary tract infections, intravenous drug abuse, genitourinary infections, dental procedures4. Diagnosis is largely clinical with supplementary investigations like vitreous tap for smear and culture ,blood cultures.

The incidence of endogenous endophthalmitis has been rising due to longer life span and long term intravenous access. Though the final outcome in these cases is not very encouraging, prompt recognition, and aggressive treatment is the key to prevent severe visual loss in these patients.

This article attempts to review and concise the epidemiology, clinical findings, and management of endogenous endophthalmitis.

Classification of Endophthalmitis

Endophthalmitis has been defined in standard text books of ophthalmology as, the Inflammation of the anterior or posterior segment or both, with involvement of the adjacent ocular wall.

The European society of cataract and refractive surgeons defines it as an inflammatory reaction occurring as a result of intraocular colonization by bacteria, fungi, or rarely parasites1. Endophthalmitis is classified as Table 1.

<table>
<thead>
<tr>
<th>Infectious Endophthalmitis</th>
<th>Sterile uveitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute post operative endophthalmitis</td>
<td>Phacocoaxanthitic endophthalmitis</td>
</tr>
<tr>
<td>Delayed onset endophthalmitis</td>
<td>Sympathetic ophthalmia.</td>
</tr>
<tr>
<td>Conjunctival filtering blee associated</td>
<td>Endogenous Endophthalmitis</td>
</tr>
<tr>
<td>Post Traumatic.</td>
<td>Post Operative</td>
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</table>

Endogenous Endophthalmitis can be classified as in Table 2:

<table>
<thead>
<tr>
<th>Anterior</th>
<th>Focal</th>
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<tbody>
<tr>
<td>Diffuse</td>
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</table>

<table>
<thead>
<tr>
<th>Posterior</th>
<th>Focal</th>
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<tbody>
<tr>
<td>Diffuse</td>
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<table>
<thead>
<tr>
<th>Panophthalmitis</th>
<th>Focal</th>
</tr>
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<tbody>
<tr>
<td>Diffuse</td>
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</table>

Epidemiology

Endogenous endophthalmitis, also termed metastatic endophthalmitis, comprises only a minority of endophthalmitis cases, with an incidence rate of 2- 15%6, Puliafito et al in their series had reported an incidence of 2-5 %.Though metastatic endophthalmitis can occur at any age, Wong et al7 and connell et al8 have reported a mean age of 55 years and 57.5 years respectively, and has no sexual predilection but some series have reported a slightly more preponderance for males at 53.8 %. The right eye is twice as often prone for a focus of infection than the left, because of the more proximal and direct blood flow to the right carotid artery1. Bilateral involvement occurs in approximately 25 % of cases8.
Risk Factors

The risk factors for endogenous endophthalmitis can be varied, and with certain geographic predispositions. Common risk factors include Diabetes Mellitus, Malignancy, lymphoproliferative disorders, G.I tract infections, Immunosuppression, parenteral alimentation, recent extended surgical procedures, alcoholism, I.V drug abuse, catheters/UTI, Endocarditis, Skin infections, Joint Infections, Hepatobiliary Tract Infections, COPD, End stage renal disorders.

Binder et al⁴, in their case series have found indwelling catheters/UTI as the primary risk factor, while Leibovitch et al⁵ had Diabetes Mellitus, COPD, End stage renal disease as the commonest risk factors. Okada et al⁶ had indocardiatis and G.I tract infections, while Essman et al⁷ found parenteral alimentation as the most common risk factor. Schielder et al⁸ in the case series of 21 patients found Indwelling catheters, Diabetes as the commonest risk factors, and PP Connell et al⁹ had a high incidence of IV drug abuse [38%] in their case series. In contrast to the above studies, Wong et al⁷ have found hepatobiliary tract infections and Diabetes as their commonest risk factors which they attributed to the higher incidence of hepatobiliary tract infections in their study population.

In our own experience with 12 cases[ 14 eyes] of metastatic endophthalmitis, with a mean follow up period of 5 months, Diabetes Mellitus[41.6 %] was the commonest risk factor, followed by liver pathology. Other risk factors were Malignancy, UTI, Liver transplant, and leukemia.

Etiology and Pathogenesis

Endogenous endophthalmitis can be caused by a spectrum of pathogens, ranging from gram positive bacteria , to rarer organisms like citrobacter and non tuberculous mycobacteria.

Since it is metastatic in nature, the source of infection is from a site distant to the eye. The pathogen spreads hematogenously to the eye. Immuno compromised states such as diabetes mellitus, malignancy, patients on immunosupression, are associated with reduced host defense and a high risk for endogenous endophthalmitis.

Retinal damage is multifactorial, which includes damage caused by microbial toxins and ischemia caused by septic emboli.

Gram positive organisms are responsible for 40% of cases⁹ and is more commonly seen in the western population¹⁰

Bacterial endophthalmitis

Gram positive bacteria

Leibovitch et al¹¹ and Okada et al have found Streptococcus spp as the commonest infective pathogen, while Staphylococcus sps was the predominant organism in Jackson TC et al¹ case series. Greenwald et al found a high incidence of Bacillus Cereus.

Hence the most common gram positive bacteria causing endogenous endophthalmitis is the Streptococcus spp.

Gram negative bacteria

Among Gram negative organisms, Jackson et al, Wong et al, and Vivian Schielder et al have reported Klebsiella as the single largest cause of metastatic endophthalmitis while Pseudomonas was the most frequent causative pathogen in the Leibovitch et al, and the Irvine WD et al¹⁴ studies. Hence the commonest gram negative organism is Klebsiella pneumoniae, followed by Pseudomonas aeruginosa. Other offenders include E.coli,Serratia Marcescens,Listeria Monocytogens,and Neisseria Meningitides.

Fungal metastatic endophthalmitis

Studies on fungal endophthalmitis have shown the preponderance of aspergillus¹¹,¹⁵ and candida¹⁶,¹⁷ as the most common pathogens.

Other causative fungi are, Pseudallecheria boydii, Histoplasma, Coccidoides, Blastomyces, Cryptococcus, Sporothrix, and Bipolar Hawanesi among others.

Streptococcus pneumoniae and s.viridans are common causes of bacterial endogenous endophthalmitis secondary to meningitis and endocarditis respectively. Group G streptococcal endophthalmitis has been reported in elderly patients with skin infections or malignant neoplasms , and group B streptococcal endophthalmitis has been noted in neonates with meningitis and in immunocompromised adults.¹⁶-¹⁸ Gram negative bacteria were found to be the most virulent ⁷.

In immunocompromised patients, intraocular infections represents dissemination of invasive diseases caused by candida species ,Aspergillus sps, Fusarium sps, Cryptococcus neoformans ,Pseudallescheria boydii and others⁹,²⁰.

In our case series, Fungal metastatic endophthalmitis[50%] was slightly more commoner than bacterial[33.3%].

Clinical Findings

Endogenous endophthalmitis can occur a week, to a month after onset of systemic complaints /sepsis. Onset of symptoms was rapid in the case series of Okada et al¹¹ and Schielder et al⁷ while it was more indolent in the Essman report.

Complaints of ocular pain, blurring of vision, ocular discharge, and photophobia , in a patient with the above risk factors, should be suspected to have Endogenous endophthalmitis. Signs suggestive of endophthalmitis include chemosis, flare
and cells in the anterior chamber, hypopyon, retinal changes such as Roth spots, and retinal periphlebitis (Figure 1). Ocular ultrasonography should be done if there is no view to the fundus, which can show vitreous opacities, exudates, membranes, retinochoroidal thickening and retinal detachment.

Systemic symptoms of sepsis include malaise, nausea, loss of appetite, and fever.

In Anterior focal disease, the anterior segment inflammation is mild, the infection is confined to discrete foci and may be seen as iris nodules or micro abscesses. On the other hand, in the diffuse type, the inflammation is more severe, with chemosis, lid swelling, corneal edema, fibrin in the anterior chamber, and hypopyon, with or without raised intraocular pressure.

Posterior focal disease presents as whitish nodules or plaques in the choroid which gradually involves the retina (Figure 2). Gram positive organisms may be multifocal, associated with Roth spots and retinal vasculitis, and tend to be severe. Gram negative infections usually cause a single large choroidal abscess involving the posterior pole9, with minimal injection of the conjunctiva, a relatively clear cornea, and mild to moderate anterior chamber reaction. Diffuse disease is more severe, with intense vitreous inflammation. Peri vascular hemorrhages inflammatory infiltrates and arterial emboli have been noted. This can further lead on to retinal necrosis, detachment and perforation. Gram negative organisms like pseudomonas and Klebsiella can cause panophthalmitis.

Candidal endophthalmitis usually starts as a focal choroiditis, gradually spreading to the retina, and breaking through to the vitreous, forming a string of pearls, characteristic of candida albicans (Figure 3).

**Diagnosis/Investigations**
1. Hb, TC, DC, ESR.
3. Chest X ray – To rule out pulmonary pathology.
4. Echocardiography – If there is a possibility of endocarditis.
5. CT/MRI/USG – Of the orbits for the diagnosis and monitoring of the response to the treatment of endogenous endophthalmitis in eyes with opaque media.
7. Vitreous and aqueous tap – For fungal and bacterial smear and culture
8. Polymerase chain reaction.
9. Semi-nested polymerase chain reaction - For rapid detection of panfungal genome directly from ocular specimens.

Aqueous tap can be obtained with a 26 G or 30 G stab incision at the limbus, aspirating 0.1 -0.2 ml of aqueous. Vitreous can be tapped using a 23 gauge needle at the end of a plastic 2cc syringe [0.2ml], through the pars plana, and intravitreal antibiotics delivered into the vitreous cavity through the same .Vitreous tap can also be done by using a 25 G 3 port pars plana vitrectomy ,with a tuberculin syringe attached to the end of the probe.

**Treatment**

The treatment of Metastatic endophthalmitis is the same as for the exogenous variety .The below given flow chart gives a overview of the line of management to be undertaken.
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Role of intravitreal antibiotics

Intravitreal antibiotics are still the first line of treatment in all cases of endophthalmitis. Antibiotics can be given empirically to cover a broad spectrum of organisms or tailored against a particular species of pathogens.

The common antibiotics used intravitreally is given in Table 3

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CONCENTRATION [mic gm/0.1 ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>400 Micro grams</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2000 Micro grams</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>5 or 10 Micro grams</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>2000 Micro grams</td>
</tr>
<tr>
<td>Ceftazidine</td>
<td>2000 Micro grams</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>2000 Micro grams</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1000 Micro grams</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>500 Micro grams</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>200 Micro grams</td>
</tr>
<tr>
<td>Methicillin</td>
<td>2000 Micro grams</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>500 Micro grams</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1000 Micro grams</td>
</tr>
</tbody>
</table>

The drugs of choice for gram positive and gram negative bacteria are ,vancomycin [1 mg/0.1 ml] and Ceftazidime [2 mg /0.1 ml ] respectively.

Role of systemic antibiotics

Since the primary focus of infection is the source of the ocular infection, empiric broad spectrum antibiotic therapy with vancomycin and an aminoglycoside or a third generation cephalosporin is warranted, in order to prevent continued bacteremia and reduce the chance of invasion of the other eye. The antibiotic therapy can be tailored depending on the culture reports. The drugs of choice against gram positive bacteria is Vancomycin, and is also preferred in patients known to abuse drugs covering the possibility of bacillus. If patients history or culture suggest a fungal infection, amphotericin B, fluconazole, oritraconazole shold be included in the treatment.

Role of intravitreal steroids

Steroids have been used in bacterial endophthalmitis, because of their potential to suppress the associated inflammation, which plays a major role to play in the ocular damage associated with endophthalmitis. Intravitreal dexamethosone in the concentration of 400 microgram in 0.1 ml has been used but is contraindicated in fungal endophthalmitis.

Systemic steroids also have a role to play in the treatment of endophthalmitis, for the reasons mentioned above.

Role of vitrectomy

Vitrectomy in cases of endophthalmitis is useful, as it decreases the pathogen load, decreases the inflammatory mediators in the vitreous, adequate sampling is obtained for micro analysis, and it also helps in speedy visual recovery of the patient.

Timing of vitrectomy is controversial, with some investigators, for example Okada et al and Yoon et al favouring early vitrectomy. PP Connell et al advocate aggressive early treatment with early vitrectomy in suspected bacterial metastatic endophthalmitis, and more conservative approach in suspected fungal cases. If a vitrectomy is performed, a 3 port pars plana complete vitrectomy is preferred over core vitrectomy. Complications like retinal detachment , hypotony and ptosis bulb can occur in cases of vitrectomy performed in an inflamed eye, and have be borne in mind. Thus , vitrectomy definitely has a role to play in infections with virulent organisms, and in infections uncontrolled by systemic and/or intravitreal antibiotics, with definite indications for vitrectomy being, worsening of signs and symptoms, rapid progression, retinal necrosis, extensive subretinal abscesses, retinal detachment.

Visual acuity results

Among bacterial metastatic endophthalmitis, Vivian Schielder et al found 50% of patients has a final visual acuity of >20/400 , and 50% PL/No PL. In the Okada et al study, 22% of patients had a visual acuity of >= 20/400, and 38% PL / No PL.

In fungal endophthalmitis, the visual prognosis seems to be better, with Essmann et al reporting >65% of their patients with a final visual acuity of 20/400 and 30% PL/No PL. PP Connell et al also have reported fungal endophthalmitis patients faring better than their bacterial counterparts.

In our experience, fungal endophthalmitis patients had a worse initial visual acuity, and also final visual acuity, compared to the bacterial cases.

Conclusion

Metastatic endophthalmitis is a rare but potentially devastating intraocular infection occurring due to hematogenous spread from a remote infectious site to the eye, resulting in intraocular colonization with inflammation, and subsequent severe loss of vision. Patients with risk factors are prone to infection, with gram negative bacterial endophthalmitis patients faring worse than other infections. Early recognition of symptoms, and signs and prompt management with intravitreal antibiotics, systemic antibiotics and steroids along with vitrectomy is the key to minimize damage, and prevent involvement of the other eye.
### Table 4

<table>
<thead>
<tr>
<th>Make Clinical diagnosis of endophthalmitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform aqueous and vitreous tap and / or vitrectomy, through pars plana, collecting samples for microbiology investigation</td>
</tr>
<tr>
<td>Inject empirical antibiotics intravitreally using combination of either vancomycin 1 mg / 0.1 ml and ceftazidime 2 mg in 0.1 ml (first choice) or Amikacin 400gm in 0.1 ml and vancomycin 2 mg in 0.1 ml (second choice).</td>
</tr>
<tr>
<td>Start systemic antibiotics empirically (Vancomycin and Ceftazidime)</td>
</tr>
<tr>
<td>Review microbiology reports and tailor antibiotics accordingly.</td>
</tr>
<tr>
<td>Improving</td>
</tr>
<tr>
<td>Worsening</td>
</tr>
<tr>
<td>Follow up</td>
</tr>
<tr>
<td>Consider referral to Vitreo retinal surgeon for opinion for full vitrectomy and repeat intravitreals.</td>
</tr>
</tbody>
</table>

Modified from ESCRs guidelines on prevention, investigation and management of post operative endophthalmitis – Peter Barry, Wolfgang Behrens-Baumann, Uwe Pleyer and David Seal Aug 2007.

### References

1. ESCRs guidelines on prevention investigation and management of post operative endophthalmitis – Peter Barry, Wolfgang Behrens-Baumann, Uwe Pleyer and David Seal. August 2007.
9. J Fernando Arevalo, Aliza Jap, Soon-Phaik Chee, David g Zeballos:


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Conf. secretariat: Aravind Eye Hospital  
Tirunelveli-627001  
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