

Recent Advances in Endophthalmitis- A Review

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Abstract

Endophthalmitis refers to inflammation of the inner coats of the eye. It is one of the dreaded complications for an ophthalmologist. It can present with floaters, ocular pain and redness, and a diminution of vision. Depending on the presence of organisms or toxins, it can be classified into infective and non-infective. Infective endophthalmitis, caused by microbes such as bacteria, fungi, viruses, and parasites, can be further subclassified, depending on the entry route, into an exogenous or endogenous approach. Endophthalmitis via exogenous route occurs when the microbes enter the sterile eye environment postoperatively (post cataract or post intravitreal injections) or post-traumatic while endogenous endophthalmitis results from the bloodstream, carrying the infection to the eye. This review aims at highlighting the recent advances in diagnosing, preventing, and treating endophthalmitis. We have gathered our information from various articles published in PubMed. Through this article, we would like to upgrade our scientific knowledge, widen our research field, and pave the way to follow newer trends to combat this grave diagnosis.

Keyword: Endophthalmitis, Quantitative PCR, Multi-mono PCR.

INTRODUCTION

Infective endophthalmitis is an emergency ophthalmic condition that can potentially permanently impair vision. In extreme cases, it might necessitate enucleation. Hence a prompt and accurate diagnosis with a higher yield with a minute sample size is the need of the hour for saving vision.

Advances in Diagnostic Techniques

The gold standard used for diagnosing the endophthalmitis is culture despite high specificity, low yield, and time-taking. For specific treatment, there is a need for molecular and genetic diagnostics.

Specific PCR and Quantitative PCR

Metagenomics refers to studying and analyzing the structure and function of whole nucleotide sequences isolated from organisms. It is a step toward 'precision medicine' wherein rapid characterization of infection guides treatment and prevention. Kosacki *et al.*¹ published a study to compare three methods of identification i.e. by standard culture, 16s rRNA pan bacterial PCR, and quantitative PCR (qPCR).

For 16s rRNA PCR, samples were amplified and then sequenced using the 'universal 16s rRNA primer sequence' common to all known bacteria. For qPCR aka real-time PCR, specific custom primers were used to perform a targeted amplification and quantification of a bacterial pathogen. In

the study rate of successful pathogen identification was as given in Table 1.

The qPCR produced results in 2 to 3 hours, 16s rRNA PCR in 2 to 3 days while culture took around 14 days to produce the result

Multi-mono PCR (mm-PCR) and High Throughput Sequencing

Van Halsema *et al.* studied a more targeted approach using mmPCR in which primers against 20 common bacterial pathogens causing infectious endophthalmitis were used for pathogen identification. A set of target genes from 20 putative bacterial pathogens were used in tandem with PCR, along with a pan-bacterial target for the 16s rRNA gene that is present in all bacteria and is not one of the 20 pathogens listed in the catalog. The mmPCR have 89% concordance with standard culture in species-level identification. The

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Table 1: Rate of successful pathogen identification

Method	Before intravitreal antibiotics (%)	After intravitreal antibiotics (%)
Standard culture	54	36
16s RNA PCR	49	48
qPCR	7	7

sensitivity and specificity of mmPCR are 91 and 94%, respectively, equivalent to culture.² mmPCR gave results within 90 minutes.

The studies were done by Gandhi *et al.*³ and Mishra *et al.*⁴ suggested high throughput technique. Both studies found a 93.3% bacterial detection rate and 100% fungi detection rate in culture-positive samples and 19.3% bacteria and 63.1% fungi grew in culture-negative samples. The time required to produce the result was 2 to 8 hours. Instead of amplifying the entire genome, they identified and selected a few highly pathogenic sequences which were amplified. This prevented amplification of the host genome, which helped in reducing confounding. The demerit to this technique is contamination due to multistep processing and high cost.

Nanopore Sequencing

In recent years, nanopore sequencing technology, a fourth-generation technology, has had a breakthrough in genomic sequencing. This owes to the development of 'long-read nanopore sequence MinIoN developed by Oxford nanopore technologies and then the sequencer PremethIoN' led to rapid pathogen detection. This technology enables single-stranded DNA or RNA to pass through nano-size holes in the artificially manufactured lipid membrane to convert the biological signal into the current signals which are interpreted by algorithms and metagenomic matching can be performed.⁵

Advances in the Prevention of Endophthalmitis

Instilling eye drops does not guarantee that the drug is reaching there and it depends too much on patients' compliance. Methods that ensure sure shot delivery of drugs into deeper parts of the eye have been devised.

Intracameral Antibiotics

Bowen *et al.* in a meta-analysis done to compare the efficacies of intracameral cefuroxime, moxifloxacin, and vancomycin in post-phacoemulsification endophthalmitis concluded that the incidence rates of endophthalmitis were as shown in Table 2.⁶

Rathi *et al.* conducted an interventional study to find out the effectiveness of intracameral cefuroxime with moxifloxacin and vancomycin in the reduction of endophthalmitis post-small incision cataract surgery in rural India, a 3.4-fold decrease in cases was seen in Table 3.⁷

Intraocular Lenses loaded with Moxifloxacin and Ketorolac

In recent years, intraocular lenses (IOLs) as a drug delivery device can replace or act as an adjuvant to eye drops in

Table 2: incidence of endophthalmitis in meta-analysis done by Brown *et al.*⁶

Intracameral injections	Incidence of endophthalmitis (%)
Cefuroxime	0.0332
Moxifloxacin	0.0153
Vancomycin	0.0106

Table 3: reduction in endophthalmitis post small incision cataract surgery in rural India as seen in study done by Rathi *et al.*⁷

Intracameral antibiotic injection	Decrease in incidence of endophthalmitis post intracameral Injection (%)
Cefuroxime	0.017
Moxifloxacin	0.049

postoperative care. The advantage is that it ensures continuous drug delivery without worrying about patient compliance. Various techniques have been used to load drugs into the IOLs, that include soaking in drug solution, supercritical solvent impregnation method, and IOL surface modification to incorporate the drug into IOL.

"The supercritical impregnation method has been widely studied since it could be applied to both hydrophilic and hydrophobic lenses and device behavior can be optimized by tuning parameters such as pressure, temperature, and solvent. The main disadvantage is the cost and complexity of the technique".⁸ For these drug-eluting IOLs, the major challenge is to establish a regulated and prolonged release of medications that meet the therapeutic demand without causing ocular toxicity to surrounding tissue or impairing the lens's physical properties.

Role of Povidone-Iodine in Preventing Endophthalmitis

Povidone iodine is used worldwide for its high antimicrobial property, absence of resistant bacteria to it, and low cost. The safe and highly bactericidal concentrations range from 0.050 to 0.500% for ocular surface washing. Repeated washing of the ocular surface with 0.25% povidone-iodine every 20 to 30 seconds during ophthalmic surgeries eliminates the conjunctival normal flora, minimizing the passage of bacteria into the intraocular compartment, and is thus useful for the prevention of endophthalmitis.⁹

The operative field was irrigated with 0.25% povidone-iodine thoroughly at the beginning, before inserting IOL, and at the end of the surgery, resulting in an extremely low bacterial contamination rate in the anterior chamber after surgery.

Advances in the Treatment of Endophthalmitis

An endophthalmitis vitrectomy study (EVS)¹⁰ conducted in 1995 concluded that patients who arrive with eyesight better than PL-positive status do not require an early vitrectomy. Maculopathy or injury to the peripheral retina caused by atrophic holes resulting from hypopyon in the vitreous cavity-causing retinal detachment leads to permanent loss

of vision in patients with endophthalmitis. Recent studies have contradicted EVS's conclusions and found a very good prognosis after early and complete vitrectomy.

Early and Complete Vitrectomy

Robert E. Morris and Ferenc Kuhn¹¹ in Alabama published a report on 10-year (2007–2017) results achieved at their retina center. High visual acuity and lower retinal detachment rates were seen after the complete and early vitrectomy (6.4 vs 8.0% in EVS).

In perception of light (PL) positive patients, “visual acuity of $\geq 20/40$ was achieved in 79% of cases vs 53% reported in the EVS.”¹¹

Of the patients presenting with hand movement or better, 88% regained $\geq 20/40$ or better vs 64% in EVS.

Early and complete vitrectomy provides a non-toxic vitreous cavity, a clear retinal surface from purulence, and antibiotic protection against microorganisms at the vitreoretinal surface.

Silicon Oil in Infection Control

The antimicrobial properties of silicon oil have been extensively investigated. It has been suggested that high surface tension and low permeability of silicon oil could limit the freedom of movement of the pathogen, concentrating them in the ciliary body or close to the retinal blood vessels where the defense mechanism could act more effectively. Moreover, the space-occupying action of a long-standing tamponade may play an important role in pathogen and toxin washout preventing damage to the retina.¹²

Role of Alternative Intravitreal Antibiotics

The first-line drugs for endophthalmitis include vancomycin (gram-positive), ceftazidime (gram-negative bacteria) and, amphotericin B, and voriconazole for fungal endophthalmitis. There has been emerging antibiotic resistance in microorganisms.¹³ Hence, there is a need to study the role of alternative antibiotics.

Alternative antibiotics for gram-positive organisms include linezolid, daptomycin, and tigecycline. Several studies showed microorganisms resistant to traditionally used antibiotics successfully treated with intravitreal alternate antibiotics.^{14,15}

Alternative antibiotics for gram-negative bacteria include imipenem and fluoroquinolones (ciprofloxacin/moxifloxacin). Dave *et al.* reported 11 cases of endophthalmitis resistant to ceftazidime treated successfully with intravitreal imipenem.¹⁶ Many clinical series demonstrated the clinical efficacy of ciprofloxacin against gram negatives, including *Pseudomonas* and synergistic effects with vancomycin.

The mainstay treatment for fungal endophthalmitis includes amphotericin B and voriconazole. Alternatives like miconazole and echinocandins have shown high potential. Minocycline was used to treat amphotericin B-resistant *Paecilomyces lilacinus* successfully.¹⁷ Intravitreal caspofungin

in the rabbit model of endophthalmitis showed potential to be used as an alternative antifungal agent with lower retinal toxicity.¹⁸

CONCLUSION

Due to the significant risk of blindness, endophthalmitis is a serious illness. At the moment, traditional culture techniques, clinical symptoms, surgical procedures, and antibiotic administration are used for its diagnosis. PCR, high throughput technique, and nanopore technique help in pathogen detection in the sample, which cannot be obtained by culture, and improves endophthalmitis pathogen detection positively to a certain extent. Through the interpretation of genetic information, the antibiotic sensitivity of an organism can be ascertained, which will help in the reduction of antimicrobial resistance. The most frequent intraocular procedure performed globally is cataract surgery. The incidence of endophthalmitis following cataract surgery and intravitreal injection is 0.4 and 0.06%, respectively. This accounts for the huge cost of the disease. Therefore, early prevention using intracameral antibiotics could help reduce the disease's burden. Eye drops have a short residence time, which results in limited drug bioavailability and the necessity for frequent instillations, which can lead to low compliance, especially in the older population. Without any further steps beyond IOL installation, IOLs equipped with antimicrobials might provide continuous administration independent of patient compliance. In acute post-cataract endophthalmitis, early and full vitrectomy has enabled the early management of endophthalmitis, controlling infection and reducing the need for eviscerations. Further studies on large-scale populations are needed to understand the role of povidone-iodine-silicone in treating endophthalmitis.¹⁹

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