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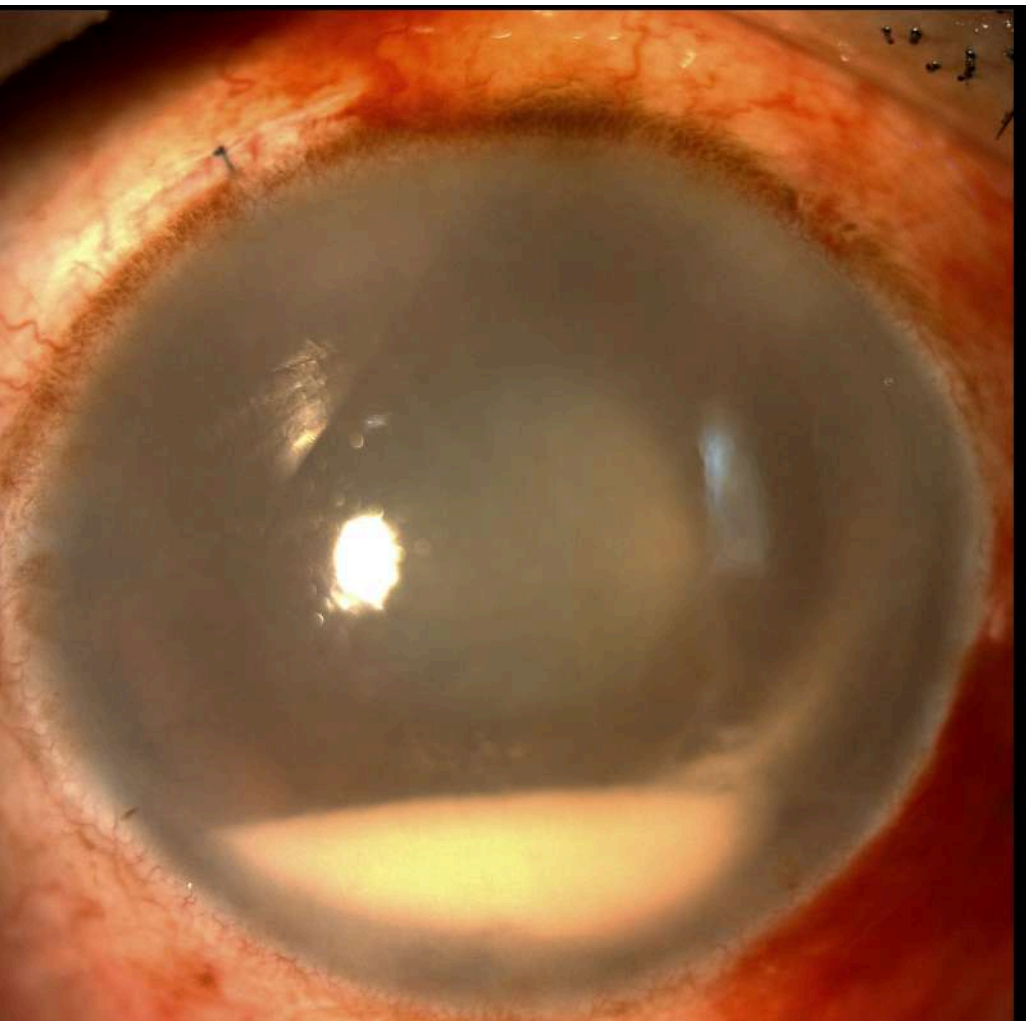
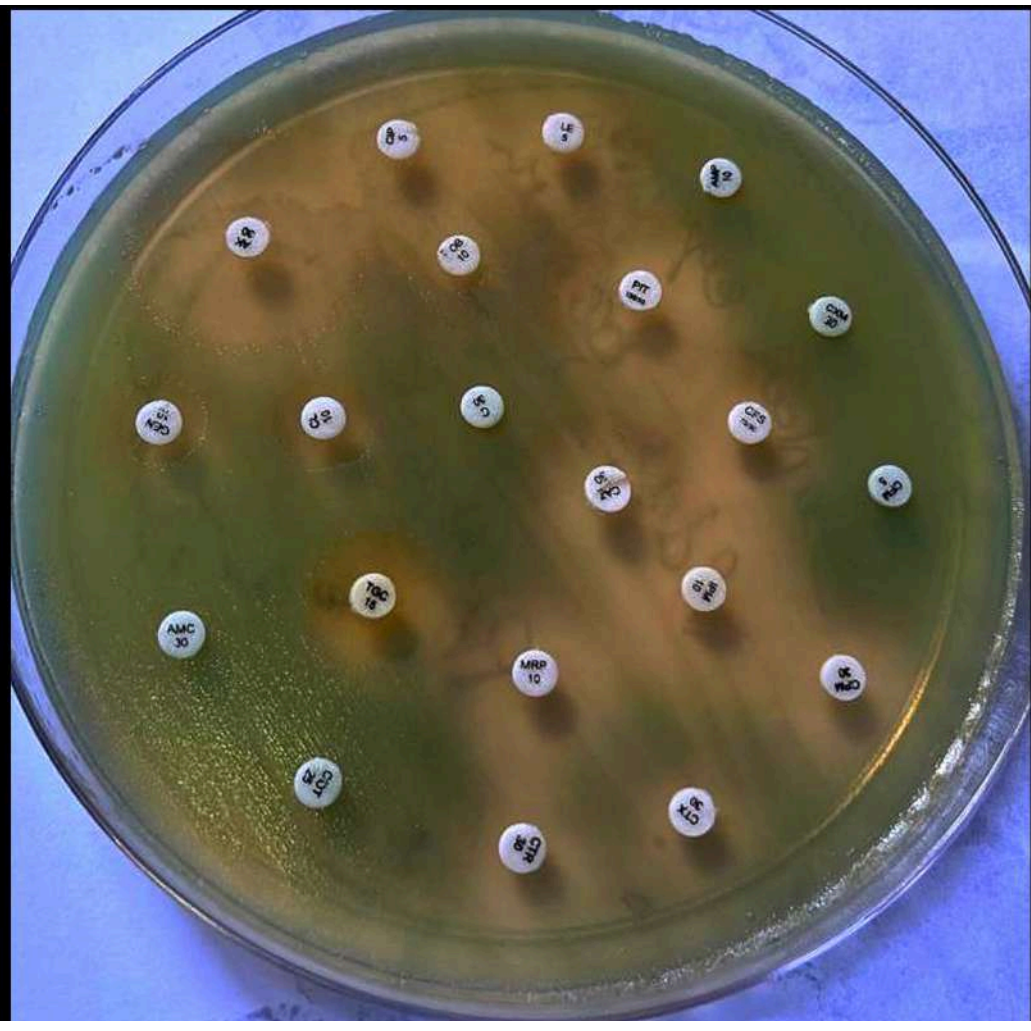
The Official Newsletter of the

VITREORETINAL SOCIETY-INDIA





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FROM THE PRESIDENT'S DESK

Dear Friends

Season's greetings to all !! This issue focusing on endophthalmitis will prove to be a handy source of reference to all us in our busy practice. Congratulations to Dr Mahesh Shanmugam and his team mate Dr Pradeep Sagar for their stupendous efforts.

The preparations for the annual conference at Trivandrum are going on in full swing. Please register and attend this conference in large numbers. A rich scientific feast awaits you and the organising team have planned to give you an awesome experience.

The awards for the annual conference have been announced. We are very happy to inform that we have instituted an award and a prize after two legends of our lifetime- Dr S S Badrinath and Dr P N Nagpal. Congratulations to the awardees ! We look forward to hearing them during our annual meeting.

Diabetic retinopathy continues to remain as the most important avoidable blindness. We need to intensify our efforts to mitigate this. VRSI and AIOS are working together to impress the Health ministry about importance of screening for DR.

Our Dynamic Secretary Dr Manisha Agarwal has spelled out all the activities of our society. Once again, I thank Dr Pradeep Sagar for a wonderful issue.

Dr N S Muralidhar

President, VRSI

FROM THE HONORARY SECRETARY'S DESK

Dear Friends,

Greetings from VRSI ! We are all aware that Endophthalmitis is the most dreaded complication for any of us to manage. This newsletter focuses on this topic. Congratulations to our scientific committee convenor Dr Mahesh Shanmugam and his team specially Dr Pradeep Sagar for the effort done in compiling this issue.

The World Diabetic day is on14th November. VRSI requests each member of the society to actively contribute in spreading awareness of Diabetic retinopathy and to conduct various activities to celebrate this day. Diabetic retinopathy is the prime focus both for VRSI and AIOS. Both the societies along with RSSDI (Research Society for the study of Diabetes in India) have formulated DR screening guidelines for Physicians. Our society has been successfully conducting DR screening and managing skill transfer workshops in various two tier cities for general Ophthalmologists and Physicians. Special thanks to Dr. NS Muralidhar, Dr. R Kim, Dr. Lalit Verma, Dr. Raja Narayanan, Dr. Rajiv Raman and Dr. Padmaja Kumari Rani for being the guiding force.

The annual conference this year is at Trivandrum hosted by Dr Unnikrishnan Nair and his team. They are working hard to make it a memorable event for all of us. However the final success of any conference depends on the scientific deliberations and discussions done by the faculty and delegates. We hope to have an active participation by all the members making it a grand success.

FROM THE HONORARY SECRETARY'S DESK

Hearty congratulations to all the award winners this year and we look forward to some great oration lectures.

Kindly block your calendar from 1st to 3rd Dec 2023 for an exciting annual VRSI conference including the scenic beauty of Trivandrum along with some great learnings……

Dr. Manisha Agarwal

Hon General Secretary- VRSI

FROM THE CONVENER, SCIENTIFIC COMMITTEE'S DESK

Dear Friends,

Greetings!

This issue of the VRSI newsletter deals with the ever important topic of endophthalmitis. Dr. Pradeep Sagar and team have done a stupendous job of putting up yet another great issue that details every relevant detail about endophthalmitis.

Topics that are of importance but not commonly detailed such as microbial spectrum and antibiotic resistance, role of PCR and other investigative tools in endophthalmitis, management of retinal detachment in endophthalmitis and role of corticosteroids have been covered excellently by experienced authors in this issue. Hopefully this issue will be of great value to all our members.

We have received a large number of interesting abstracts for the forthcoming meeting and the process of selection is almost complete. The list of selected abstracts will be announced soon. The conference program is shaping up slowly and we hope to have another useful and interesting conference with all your help.

Thank you for all your support and encouragement.

Dr. P. Mahesh Shanmugam

Convener, Scientific Committee, VRSI.

GUIDELINES:
MANUSCRIPT SUBMISSION FOR VRSI NEWSLETTER

Original Articles :

These include randomized controlled trials, interventional studies, studies of screening and diagnostic test, outcome studies, cost effectiveness analyses case-control series, and surveys with high response rate. The text of original articles amounting to up to 3000 works (excluding Abstract, References and Tables) should be divided into sections with the headings: Abstract, Key-words, Introduction, Material and Methods, Results, Discussion, References, Tables and Figure legends.

Case Reports / Challenging Case / Innovations / Instruments / Techniques:

New, interesting, challenging, rare cases, innovations, instruments and techniques can be reported. They should be unique and providing learning point for the readers. Manuscripts with clinical significance or implications will be given priority. These communications could be of up to 1000 words (excluding Abstract and References) and should have the following headings : Abstract (unstructured), Key-words, Introduction, Case, Discussion, Reference, Tables and Legends in that order. The manuscript could be supported with up to 10 references. Case Reports could be authored by up to four authors.

Mail to : convenervrsi@gmail.com (or)

pradeepsagarbk@gmail.com

COVERPAGE IMAGE

Dr. Harshal Sahare

Dr. Ravishankar HN

Department of vitreo-retina, Sankara eye hospital, Shimoga

Dr. Santosh Patil

Department of Microbiology, Nanjappa hospital, Shimoga

A 66-year-old lady presented with chief complaints of pain, redness and watering in the right eye, 2 days following phacoemulsification with IOL implantation. Slit-lamp examination revealed generalised conjunctival congestion with an exposed tunnel site with suture in place and no evidence of infiltration. Anterior segment examination showed corneal edema, 3 mm hypopyon and fibrinous membrane in anterior chamber (**left image**). A diagnosis of acute post-operative endophthalmitis was made. Vitreous tap was performed and intravitreal antibiotics (Vancomycin 1mg + Piperacillin/ Tazobactum 225 µg) were administered. Polymerase chain reaction was positive for Pseudomonas aeruginosa, and Tryptic Soy Agar culture results indicated the presence of pseudomonas colonies (greenish growth) with variable growth encircling the antibiotic tablets (**right image**). The organism was sensitive to Ciprofloxacin, Levofloxacin, Amikacin, Piperacillin/Tazobactum, Cefaperazone/Sulbactum, Imipenem, Meropenem, Colistin and resistant to Ampicillin, Ceftazidime, Cefixime, Ceftriaxone.

MICROBIAL SPECTRUM AND ANTIBIOTIC RESISTANCE IN ENDOPHTHALMITIS– CURRENT SCENARIO

Dr Navya Cherukuri*

Smt Kanuri Santhamma Center for Vitreoretinal Diseases

Anant Bajaj Retina Institute, L V Prasad Eye Institute, Hyderabad

*Corresponding author

Dr Mudit Tyagi

Smt Kanuri Santhamma Center for Vitreoretinal Diseases

Anant Bajaj Retina Institute, L V Prasad Eye Institute, Hyderabad

Microbial spectrum and antibiotic resistance in endophthalmitis are usually known to change over a period of time. It is also known to vary based on geographic locations. Evolution of aseptic measures, change in surgical procedures and environmental conditions and a change in antibiotic usage can, all together, influence the microbial spectrum and its resistance.[1]

Gram positive bacteria are the most common organisms causing endophthalmitis in India accounting for 67.7% of total bacteria while 32.3% are gram negative organisms. Over a period of 25 years, it was noted that there is decreasing trend in coagulase negative staphylococci from 42% in 1991 to 29% in 2015 and increasing trend in streptococcus species.[1] This study (conducted in India and published in 2019) reported that gram positive organisms are susceptible to vancomycin (96%) and fluroquinolones like gatifloxacin (89%). The resistance to ceftazidime has increased from 31% in 2005 to 62% in 2015 and to amikacin decreased from 36% in 2005 to 33% in 2015.[1]

Studies from India have also shown increasing resistance to ceftazidime and fluoroquinolones and decreasing resistance to imipenem and aminoglycosides.[1] This becomes important because ceftazidime is the usual empirical antibiotic used to cover gram negative bacteria and its increasing resistance is a major concern.

In a study by Liu C et al (conducted in East China and published in 2021),[2] gram positive bacteria accounted for 82.5% while 17.5% were gram negative. Coagulase negative staphylococci (CONS) and Pseudomonas aeruginosa were the most commonly isolated gram positive and gram negative bacteria respectively.[2] Methicillin resistance was observed in 46.4% of Staph aureus and in 61.1% of CONS.

ARMOR study (conducted in USA and published in 2022) noted two fold increase in methicillin resistance among Staph aureus (41%) and CONS (46.3%).[3] It is postulated that antimicrobial resistance develops due to mutations in genes associated with drug target sites and transfer of foreign DNA containing resistance determinants.[4]

Yap A et al[5] reported lower incidence of antimicrobial resistance in their study (conducted in Auckland, New Zealand and published in 2023). They recommended local protocols which can prevent development of antimicrobial resistance. These include

avoiding topical antimicrobials before and after intravitreal injections, judicious use of topical or oral antimicrobials for ocular infections and intracameral cefuroxime following cataract surgery as prophylaxis instead of postoperative topical antimicrobial agents.

Antimicrobial resistance is also associated with higher rates of retinal detachment. Antimicrobial resistant strains cause more inflammation and destruction of infected retina compared to susceptible strains. Virulence factors are genetically transferred along with resistance vectors and accumulate in longer surviving bacteria.[6] Such bacteria are capable of ocular tissue invasion, breaking down blood retinal barrier and triggering destructive immune response.[7]

Louise J. Lu et al[8] (conducted in USA and published in 2020) compared microbial spectrum and antibiotic resistance in endophthalmitis from previous years and noted increasing resistance of CONS with 100% of isolates exhibiting resistance to at least 2 antibiotics tested and 77% of isolates exhibiting resistance to at least 3 antibiotics. They noted increase in incidence of endophthalmitis secondary to gram negative bacteria. Previously Pseudomonas aeruginosa was insignificant cause of endophthalmitis, but over a period of time it is reported to be comprising of 10.6% of overall microbial spectrum.

In a 25 year study by Gentile RC et al. (conducted in New York and published in 2014),[9] CONS was the most frequently identified organism causing endophthalmitis. There was no significant change in microbial spectrum over 25 years in their study. They reported that vancomycin and ceftazidime are still the excellent empirical antibiotics for endophthalmitis. They noticed increasing resistance to cephalosporins and methicillin and decreasing resistance to aminoglycosides and imipenem.

In conclusion, though there is not much difference in microbial spectrum and resistance

pattern of antibiotics in the west over a period of time, in India, there is increasing incidence of gram negative bacteria and also increase in resistance patterns of these organisms.

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POLYMERASE CHAIN REACTION [PCR] AND NEWER INVESTIGATIVE TOOLS IN ENDOPHTHALMITIS

Dr A R Anand

L & T Microbiology Research Centre

Medical Research Foundation, Chennai

Dr Jyotirmay Biswas

Department of Uveitis

Medical Research Foundation, Chennai

Introduction

The rapid and accurate laboratory identification of the etiology of infectious endophthalmitis has critical implications in therapeutic and potential surgical management.[1] Conventional microbiological investigations include direct microscopy and culture of intra-ocular fluids, with the latter continuing to be the gold standard in lab diagnosis of endophthalmitis. However, isolation of bacteria/fungi from intra-ocular specimens is time-consuming and lacks sensitivity. The low culture positivity could be due to various factors such as prior antibiotic treatment, presence of fastidious

organisms and delayed sample processing. This has created a need for a more sensitive and rapid method to detect microbes in endophthalmitis. In recent years, the diagnosis of infectious diseases in clinical practice, including endophthalmitis, has been revolutionised by the application of molecular techniques, particularly Polymerase chain reaction (PCR). These new molecular diagnostic tests are highly sensitive, specific, and rapid, requiring very small volumes of sample and have significantly increased the etiological diagnosis in culture-negative specimens. A brief overview of the newer molecular techniques that are being used and evaluated in the diagnosis of infectious endophthalmitis is given below.

Polymerase Chain Reaction (PCR)-based assays

PCR is a technique whereby theoretically a single or a few copies of a specific piece of DNA are amplified across several orders of magnitude, generating millions of copies of that specific DNA fragment, which in turn can be analysed easily. In the past two decades, PCR-based assays have been used extensively to discriminate infectious from noninfectious causes of intraocular inflammation and for identification of the causative agents. We and others have shown PCR to be highly sensitive and specific test for detecting specific organisms such as cytomegalovirus (CMV), Herpes simplex virus (HSV), Varicella zoster virus (VZV), *Toxoplasma gondii* as well as *Mycobacterium tuberculosis.*[2-6] Endophthalmitis, unlike many infections in other sites of the body, is caused by a diversity of bacteria and fungi. Hence instead of using PCR to target specific organisms, broad-range PCRs are preferred. Broad-range PCRs involve the detection of any bacterial or fungal genomic DNA in the sample. We and others have used both bacterial ribosomal DNA genes (16S rDNA) or fungal ribosomal DNA genes (18S or 28S rDNA) as targets for broad-range PCR performed on ocular fluids of patients with infectious

endophthalmitis.[7-10] Broad-range PCR techniques use primers and probes that target regions in the DNA that are conserved among all bacteria (16S rDNA) or fungi (18S or 28S rDNA) and can provide information if the endophthalmitis is bacterial or fungal. Moreover, recent findings have indicated that PCR can provide a microbiology diagnosis in approximately 44.7–100% of culture-negative endophthalmitis cases.[11]

Several variations of the conventional broad-range PCR have been evaluated. These include nested PCR, real-time PCR and multiplex PCR. Nested PCR (nPCR) combines two successive PCRs with two sets of primers, allowing further amplification of a larger amount of the target DNA. Although highly sensitive, nPCR is associated with a higher risk of false-positive results due to laboratory cross contamination. Real-time PCR, also known as quantitative polymerase chain reaction (qPCR), is a variation of PCR that can be used to quantitate the number of pathogen DNA copies in the sample. The quantification of copy numbers by real-time PCR will not only help in determining pathogen load, but also to differentiate true- positives and false positives. Recently real-time PCR primers and probes for bacterial 16S rDNA and fungal 18S/28S rDNA amplifications have been evaluated in infectious endophthalmitis.[12,13] Multiplex PCR is a variation of PCR that can target and amplify multiple target genomic DNAs in one assay, unlike a classic uniplex PCR which can measure only one target genomic DNA. In-house multiplex PCR tests have been used for simultaneous detection of several bacterial or fungal species, or both.[14]

Limitations of PCR-based assays:

Molecular techniques such as PCR are not without its limitations. The high sensitivity of PCR can turn out to be a double-edged sword. Contamination of the sample with even a small amount of bacterial or fungal DNA can lead to false positive results. False positive

rates of up to 5% have been reported in the use of PCR for organism identification. False negative results can also occur due to a low microbial load, low DNA extraction efficiency or the presence of DNA polymerase inhibitors (especially hemoglobin). To overcome this, laboratories should strictly follow procedures and quality assurance protocols to ensure reliability of results. In addition, unlike culture, PCR cannot differentiate between viable and non-viable organisms. PCR detection techniques still cannot provide accurate information on antibiotic susceptibility of the organism detected. In addition, molecular techniques also have not yet been made cost-effective and requires expensive infrastructure and specific skill sets to perform and interpret.

DNA Sequencing: Sequencing, which involves determination of the sequence of nucleotides in the DNA of the organism, can help identify microbes. Both the traditional Sanger sequencing as well as the recently developed next-generation sequencing have been used to detect infectious etiology in endophthalmitis.

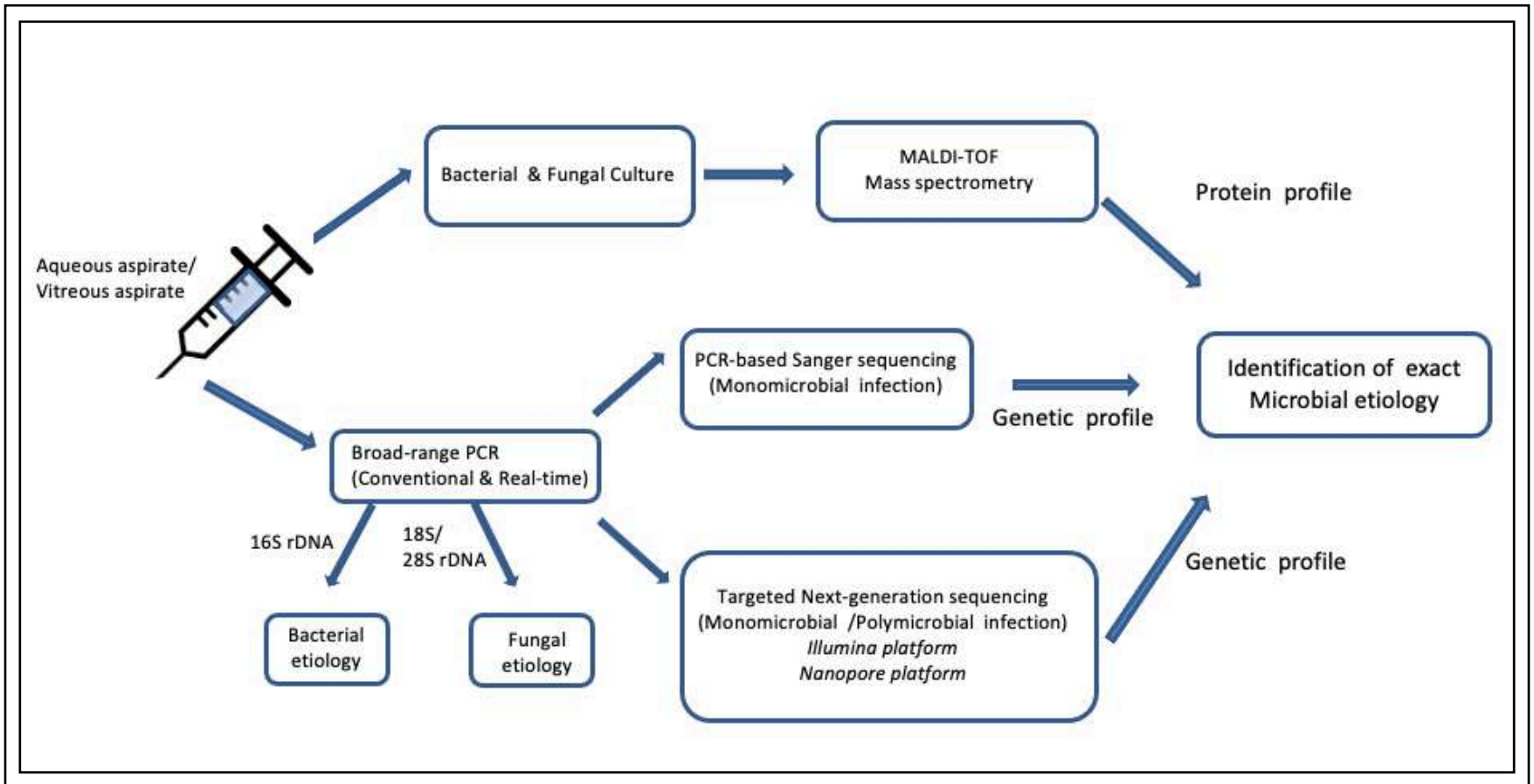
Sanger sequencing: The 16S rRNA 18SrRNA/ITS genes comprise several conserved regions interspersed by variable regions which are genus-specific or species-specific. Therefore 16S rRNA and 18SrRNA/ITS amplification combined with sequencing have the advantage of covering the entire bacterial/fungal spectrum and their subsequent identification. Sanger sequencing is very useful to amplify 16SrRNA regions of a single bacterial isolate or a clinical sample with significant load of a single bacterial/fungal aetiology. However, Sanger sequencing has low sensitivity, often giving erroneous results and becomes problematic in identification if etiology is polymicrobial.

Next generation sequencing (NGS)-based sequencing: NGS, also known as deep or parallel sequencing, is a high-throughput methodology that enables rapid and

simultaneous sequencing of different DNA fragments and is increasingly used in microbe detection and identification.[15,16]

In endophthalmitis, targeted NGS has been evaluated more commonly than non-targeted NGS. This refers to the selective capture or amplification of specific genomic regions of interest prior to massive parallel sequencing. The most commonly used strategy is the PCR amplification of 16S rRNA targeting the hypervariable regions (V1–V9) in bacteria and the ITS2 region in fungi, followed by NGS of the resulting amplicons. Targeted NGS has better sensitivity and specificity along with ease of downstream analysis and a lower cost, by allowing more samples to be tested in one run . Targeted NGS using various platforms such as Minion (Oxford Nanopore), MiSeq (Illumina) and Ion torrent (Thermofisher) have been successfully evaluated in the diagnosis of endophthalmitis.[17-20]

MALDI-TOF MS: Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF MS) mass spectrometry (MS): represents a revolution for rapid and precise pathogen identification in clinical laboratories. MALDI-TOF MS laser ionizes whole cell extracts from colonies grown in culture to produce a peptide fingerprint profile, and compares the profile against a proteomic database to identify a pathogen to a species level. MALDI-TOF MS is being used increasingly in endophthalmitis cases where there is already positive organism growth from cultures.[21,22] However, we are awaiting advances in technologies to increase the sensitivity of MALDI-TOF MS to directly identify from intraocular fluids.



Overview of the molecular techniques used in the diagnosis of infectious endophthalmitis

Conclusion

In summary, molecular methods, especially PCR assays provides a prompt, sensitive, and specific molecular diagnosis of pathogenic microorganisms associated with endophthalmitis. PCR is being used as a complementary technique to detect and identify infectious etiology, along with conventional culture methods. The arrival of newer technologies like metagenomic sequencing and MALDI-TOF-MS have shown promise in accurately detecting and identifying the causative organism in endophthalmitis.

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ROLE OF INTRAOCULAR ANTIBIOTICS IN ENDOPHTHALMITIS

Dr Avinash Pathengay

L V Prasad Eye Institute, Visakhapatnam

Dr Rudvij Pandya

L V Prasad Eye Institute, Visakhapatnam

1. Why intraocular antibiotics (IOAB) are preferred over systemic/topical antibiotics in the management of endophthalmitis?

   Historically, before the advent of intravitreal usage of antibiotics in the management of endophthalmitis, systemic antibiotics was the accepted norm in the management of endophthalmitis. When the desired outcome was not achieved, it was found that intravitreal administration of antibiotics would achieve a desired concentration in a shorter period of time which favored improved outcome in the management of endophthalmitis.[1] With this experience there was a paradigm shift

in the management of endophthalmitis. Systemic antibiotics also can achieve a desired concentration inside the eye but it takes a longer time for it. So, the initial antibiotic effect that is desired would not happen. Also, the bioavailability of the systemically administered drug is unpredictable making it just an adjuvant therapy in the management of endophthalmitis and not the primary management. However, there are some clinical scenarios where systemic anti-microbial agents have been found to have a primary role in the management of endophthalmitis especially in cases of endogenous endophthalmitis. Hence, the role of systemic antibiotics is for prophylaxis and adjuvant therapy in the management of endophthalmitis.

2. Why do you need empirical antibiotics in the management of endophthalmitis?

There are 3 reasons why empirical antibiotics have to be considered in the management of endophthalmitis,

A. Clinical presentation of endophthalmitis does not help us in identifying an etiological agent responsible for development of endophthalmitis.

B. Microbiologic culture positive rate in India in the current era is still considerably low in cases of endophthalmitis. One large study from India reviewed all cases of infectious endophthalmitis over a period of 25 years. They found that culture results were positive in 35.38% in their patients.[2] In a study among patients of endogenous endophthalmitis, deep vitreous biopsy under air was used to increase the yield from the sample. In their study, conventional anterior vitreous biopsy group had shown to have culture positivity in 30.71%, while a deep vitreous biopsy

taken under air had a culture positivity of 65.9%.[3] Thus, suitable broad-spectrum antibiotic covering wide range bacteria should be used as empirical therapy in the management of endophthalmitis.

C. Conventionally, after the vitreous sample is taken, it is inoculated on to culture media and then incubated. If there is bacterial growth, an antibiotic susceptibility test is then initiated. Thus, results of antibiotic susceptibility results are available only 36 to 48 hours after the initial inoculation.[4]

3. What are the most followed empiric antibiotic agents in the management of endophthalmitis? What are the limitations of current empirical therapy and what are the alternatives to common first line therapy?

Conventionally, the most followed empirical antimicrobial agent against gram-positive bacteria is vancomycin (1 mg/0.1ml)[5] while ceftazidime (2.25 mg/0.1 ml) is the most used empirical drug against gram-negative bacteria based on the literature from the west.[6]

Amphotericin-B (5 µg/0.1 ml) in the first line empirical anti-fungal drug conventionally.[6]

Although majority of gram-positive isolates are still susceptible to vancomycin, resistance or decreased susceptibility to vancomycin is not unheard of. There can be rare instances based on the antibiotic stewardship proposed by different labs there can be different organism like Bacillus[7] and Enterococcus[8] which may be resistant to vancomycin. In the clinical setting of vancomycin resistant organisms, intravitreal and/or systemic Linezolid can be used as second line drug for gram

positive isolates in the management of endophthalmitis.[8,9]

It is also important to understand that in countries like India which shows emerging drug resistance pattern, the usage of ceftazidime as a first line empirical drug in the management of endophthalmitis is questionable.[10,11] Keeping the sensitivity pattern of the gram-negative isolates as a reference point, determination of an empirical therapy for gram negative organism is prudent. Having said that there have been instances where alternative drugs to ceftazidime like Imipenem and colistin as an empirical drug has been associated with increased sensitivity in the management of endophthalmitis associated with gram-negative isolates.[10,11] In the setting where there is emerging drug resistance in countries like India among gram negative isolates, an alternative to ceftazidime in Imipenem/colistin may be considered in the management protocol of endophthalmitis.

As for fungal isolates, we like to combine voriconazole (100 µg/0.1 mL) routinely with amphotericin-B due to their synergistic mechanism of actions against the fungal cell wall which would help us reduce the limitations of current empirical therapy which are: fungistatic nature of the available drugs, development of resistance, poor intraocular penetration and lack of susceptibility testing.[12]

4. What are the key factors influencing the pharmacokinetics of intravitreal antibiotic injection, and how do they contribute to drug distribution, clearance, and overall effectiveness in treating endophthalmitis?

Intravitreal antibiotic injection bypasses ocular barriers, diffusing freely in the vitreous cavity to reach the retina aided by extraocular movements. Factors such as

drug properties, surgical status, inflammation, and half-life influence drug distribution and clearance. Drug elimination follows first-order kinetics proportional to drug amount and vitreous volume. Key factors influencing intravitreal antibiotic pharmacokinetics include:

Route of Exit: Large drug molecules passively diffuse anteriorly or use the posterior route via active transport. Cationic drugs exit via anterior chamber, while anionic drugs exit via uveal blood flow, influenced by the retinal pigment layer pump.

Ionic Nature: Cationic drugs like vancomycin clear via passive diffusion, while anionic drugs like beta-lactams clear more rapidly via the posterior route. Fluoroquinolones, being zwitterions, clear via both routes.

Solubility Coefficient: Lipophilic antibiotics diffuse passively, while water-soluble antibiotics clear via active transport.

Inflammation: Non-inflamed eyes clear anteriorly eliminated drugs faster; inflamed eyes show extended clearance for posteriorly cleared drugs.

Surgical Status: Clearance differs in aphakic and vitrectomized eyes. Silicone oil-filled eyes exhibit prolonged drug retention due to limited space.

Molecular Weight: Drug retention increases with relative impermeability. Drugs <500 Da have a half-life <72 h, requiring repeat injections.

Vitreous Liquefaction: Liquefaction near the globe's anterior and posterior regions accelerates drug egress, shortening half-life.

Solution Density: Denser solutions settle, causing localized toxicity, potentially requiring head repositioning.

Administration Frequency: Clinical response, half-life, clearance, and surgical status dictate dosing frequency. Repeat dosing aims to maintain drug exposure above MIC, favoring frequent injection of IOAB over administering high doses.[13]

Future trends suggest improved drug delivery systems for posterior segment diseases, enhancing drug penetration, efficacy, and patient compliance. Antibiotic resistance arises from improper use, guiding antibiotic choice based on culture and susceptibility patterns. Combination therapy requires understanding physicochemical interactions. Diligent preparation and adherence to aseptic protocols maintain antibiotic potency and stability.

5. When do you repeat IOAB in the management of endophthalmitis?

The clinical settings where one has to repeat IOAB are recurrent or persistent endophthalmitis. Recurrent or persistent endophthalmitis can be associated with organism that can be sequestered or slow growing organism like Nocardia[14] or Fungus[12] which would require prolong or multiple IOAB injections.

The aim of repeat IOAB injection is to maintain an adequate minimum inhibitory concentration in the vitreous cavity. Factors affecting the repeat injection of IOAB are the clinical response, state of the vitreous (intact vs vitrectomized), phakic/ aphakic status, half life of the injected drugs and the drug clearance from the eye[13]. Generally, we wait for 48 hours to judge the response of the IOAB and to consider a repeat injection.

6. How to identify and prevent IOAB toxicity?

In cases where there is no clear view to the retina, it becomes very difficult to establish antibiotic toxicity. But in cases where view to the retina is good antibiotic toxicity can be recognized as perivascular exudates, soft exudates, hemorrhages, retinal whitening and pruning of retinal vessels, first on the posterior pole. This can be recognized on optical coherence tomography as loss of foveal depression with diffuse retinal thinning and increased reflectivity of the nerve fiber and ganglion cell layers in an acute setting.[15]

One should understand that drugs if given beyond their established safety limits can cause retinal toxicity. And even repeated intravitreal injections can cause drug toxicity. Thus, a high level of suspicion should be kept in such cases.[16]

7. What are the concerns with antimicrobials like fluoroquinolones and voriconazole?

   Though having a broad-spectrum coverage against micro-organisms, intraocularly administered fluoroquinolones and voriconazole have extremely short half-life (Ciprofloxacin-3.5 to 5.5 hours,[17] Moxifloxacin- 1.72 hours,[13] Voriconazole - 2.5 to 6.5 hours.[18]). The half-life is even shortened in vitrectomized eyes and aphakic eyes, [13] necessitating frequent repeated administration to maintain adequate intravitreal concentration.

8. Does administering IOAB in the capsular bag help in managing delayed post-operative endophthalmitis?

   Administration of the intracapsular antibiotics in delayed postoperative endophthalmitis is one of the proposed modalities of treatment. It is also reported

that patients who have capsular bag administration of antibiotics have had recurrence of infection and associated inflammation. Hence the practice pattern may be varied based on individual experiences in administration of intracapsular antibiotic. We generally like to manage these cases in a step wise manner, first step being vitreous biopsy which includes partial posterior capsulectomy with intravitreal antibiotics and if still the inflammation persists, we consider IOL explantation with intravitreal antibiotics.[19]

9. Dose adjustments in various clinical scenarios?

When delivering intravitreal antibiotics to neonates and individuals with hypermetropic eyes, a recommended approach involves employing a diminished dosage-specifically, half of the conventional amount. This cautious approach acknowledges the smaller-than-average vitreous cavity in such circumstances.

Hegazy et al. revealed a notable retinal toxicity arising from standard intravitreal antibiotic doses in eyes filled with silicone oil.[20] This toxicity was attributed to a decrease in the available preretinal space, causing the drug to be confined within the constricted aqueous-filled area surrounding the oil bubble. Consequently, this confinement led to an extended drug elimination period. As a precautionary measure against such retinal toxicity, it is recommended employing only a quarter of the normally injected dose.

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CORTICOSTEROIDS IN ENDOPHTHALMITIS – GAME CHANGER OR DOUBLE EDGED SWORD?

Dr Naresh Babu Kannan

Department of retina and vitreous

Aravind Eye Hospital, Madurai

Dr Muthukrishnan V

Department of retina and vitreous

Aravind Eye Hospital, Madurai

Dr Athul Puthalath

Department of retina and vitreous

Aravind Eye Hospital, Madurai

Endophthalmitis is a vision threatening inflammation secondary to intraocular colonization of micro-organisms. It demands prompt identification of the infectious agent and an expedient strategy to ensure the best visual outcome.[1] The infection is typically acquired from external sources and is often associated with intraocular surgery, intravitreal injections, corneal ulcer or penetrating trauma.[2] A minority is precipitated by hematogenous spread of pathogen referred to as endogenous endophthalmitis.[3]

Endophthalmitis poses a significant burden on public health leading to potential visual loss and reduced quality of life. The incidence of acute endophthalmitis following cataract surgery is about 0.04%.[4] Typical constellation of clinical features include ocular pain, redness and decreased vision.[5] The decline in visual function results from an interplay between release of toxins the by infectious agents and immune response triggered by the host.[6]

To date, Endophthalmitis Vitrectomy Study (EVS) remains the mainstay of treatment algorithms. The advent of minimally invasive vitrectomy and newer generation fluoroquinolones have resulted in enhanced visual outcome.[7] It is postulated that though antibiotics keep the infectious organism in check, the co-existing inflammation demands an equivalent attention. The prospects of corticosteroid therapy in endophthalmitis are debatable and necessitates further research.

Corticosteroids inhibit myriad of mediators in the inflammatory pathway, effectively combating inflammatory sequelae. Therapy limits the targeting of immune cells by reducing prostaglandin synthesis and mitigating oxidative damage.[8] Steroids can be delivered via systemic, intravitreal or topical route, with oral steroids traditionally being a part of initial management protocol. All patients in the EVS group received intravitreal antibiotics, oral and topical steroids. Intravitreal steroids were not administered. EVS

suggested dosage of 1 mg/kg oral prednisolone and further recommended initiation of corticosteroids one day after the intravitreal antibiotic therapy.[7] The systemic delivery of prednisolone exhibits effective ocular penetration.[9]

The quality of life of patients who undergo enucleation or evisceration tends to be dismal, with 40% discontinuing leisure activities.[10] Furthermore, this translates into escalating rates of depression and anxiety due to concerns related to cosmetic blemish.[11,12] Therefore, preserving the eye offers psychosocial benefits despite significant visual compromise. In the most severe cases of endophthalmitis with poor prognosis, systemic steroids can salvage the eye.[13] Nevertheless, injudicious administration of steroids without counteractive antibiotic measures can lead to a considerable dilapidation and loss of the eye.[14]

Conrady et al. hypothesized that higher dose and extended taper regimen of systemic steroid could enhance resolution, especially in those with worse baseline visual acuity and post-trabeculectomy infections. Steroids may potentially reduce the ocular structural damage and decrease the likelihood of unsalvageable eyes that eventually become phthisical.[15] The patients receiving oral steroids demonstrated a significant visual improvement of three or more lines after the resolution of infection.[16] In 1989, Koul et al. demonstrated that the use of both oral and topical steroids resulted in better visual outcomes compared to topical steroids alone.[17]

The disruption of blood-ocular barrier in endophthalmitis favours the entry of inflammatory cells and mediators. It is plausible that systemic immune suppression might result in reduced intraocular inflammation.[18,19] The immunosuppressive effect of systemic corticosteroids involve distinct mechanisms, not observed in case of topical or intravitreal corticosteroids.[20]

Systemic corticosteroids may result in hypertension, metabolic syndrome and secondary lipodystrophy.[21,22] To circumvent these undesirable effects, several studies have investigated the efficacy of intravitreal steroids, the results of which have been predominantly inconclusive.[23-26] A Cochrane review unveiled insufficient evidence to validate the use of intravitreal corticosteroids in postsurgical endophthalmitis.[23] Other studies have produced conflicting results regarding visual outcome.[25,26] Intravitreal dexamethasone has a short half-life of 5.5 hours, making it unlikely to exert a significant impact on a severe persistent inflammation like endophthalmitis.[27]

Zacks et al. showed that intravitreal dexamethasone resulted in early reduction of inflammation but failed to demonstrate an independent impact on final visual outcome. However, intravitreal corticosteroids hold potential benefits in patients with medical contraindications to oral steroids.[28]

Co-administering intravitreal antibiotics with dexamethasone offers advantages of reducing the inflammatory burden and preserving the integrity of ocular tissues.[24] Both intravitreal dexamethasone and triamcinolone acetonide have been studied as supplements to antibiotics.[29] However, dexamethasone is more commonly employed due to its rapid clearance from the eye. The standard dosage is 400 micrograms and higher doses have been shown to precipitate damage to Müller cells in animal studies.[30]

Intravitreal triamcinolone may offer an optimal approach due to its ability to deliver a high initial dose. The prolonged effectiveness of triamcinolone could result from its limited solubility within the eye.[31] However, intravitreal triamcinolone has been associated with non-infectious endophthalmitis.[32] Another group has suggested that such primary complications can be appropriately managed, provided the patients are closely monitored.[33]

Compounding the complexity, concern prevails regarding effects of intravitreal corticosteroids in fungal endophthalmitis or mixed flora.[34] There is ongoing debate about the potential susceptibility of steroids in triggering fungal infections, impact on neutrophils and effect on the pharmacokinetics of intravitreal antibiotics.[33] According to a meta-analysis conducted by Soekamto et al. intravitreal dexamethasone did not yield additional visual benefits in endophthalmitis.[35]

Another aspect worth considering is that the older evidence concerning intravitreal steroids stems from a time when the initial intravitreal treatment often involved antibiotics with or without steroids, while closely monitoring the resolution pattern and making guarded decisions regarding vitrectomy based on the clinical judgment. However, the current clinical practice is increasingly favouring early vitrectomy after prompt reduction of the infectious load. In such scenarios, intravitreal steroids may be contemplated as part of the re-treatment protocols.[36]

The potentiality of corticosteroid in endophthalmitis needs to be explored since the utility of adjunctive steroid therapy still looms in controversy. There is insufficient evidence to endorse the use of corticosteroids as a standard therapeutic approach in endophthalmitis. It is imperative that larger randomized trials are conducted on this regard. However, the prudent use of corticosteroids after the infection has been adequately addressed can provide a gratifying outcome.

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MANAGEMENT OF POST-OPERATIVE ENDOPHTHALMITIS: AN EVIDENCE-BASED APPROACH

Dr Jayanti Singh

Sadguru Netra Chikitsalaya, Chitrakoot

Dr Alok Sen*

Sadguru Netra Chikitsalaya, Chitrakoot

*Corresponding author

Introduction

Post-operative endophthalmitis (POE) is a rare but severe complication of cataract surgery. The reported incidence of post-cataract surgery endophthalmitis (PCE) ranges from 0.02% to 0.71%.[1,2] The Endophthalmitis vitrectomy study (EVS)[3] recommendations guided the standard treatment for this condition for over two decades. With the

evolution of micro-incision vitrectomy systems (MIVS), PPV as a primary intervention has become safer and more accessible.[4] It has led to a debate on whether our approach to managing PCE needs to change, particularly with the increasing issue of antibiotic resistance and changes in the microorganisms that cause this condition.[5]

Endophthalmitis vitrectomy study (EVS, 1995)[3]

The management of PCE currently follows the guidelines set by the EVS, a Randomised Clinical Trial conducted in the United States and was published in 1995. The study recommended three fundamental principles for managing POE: (a) all patients must undergo microbiological evaluation through vitreous/aqueous Tap, (b) all patients must receive empirical intravitreal antibiotics, specifically vancomycin and ceftazidime, and (c) the decision for primary pars plana vitrectomy should be based on the patient's presenting vision. A vitreous tap with intravitreal antibiotics was recommended if the presenting vision was hand motions or better, and if the vision was light perception or worse, vitrectomy was suggested. The EVS indicated that diabetic patients might benefit from vitrectomy regardless of their presenting visual acuity, although statistical significance was lacking, making either tap and inject or PPV appropriate. The study also concluded that systemic antibiotics did not provide additional benefits if intravitreal antibiotics were given.

What has changed since EVS?

Microbiological profile and antibiotic sensitivity

According to the EVS, acute PCE is most commonly caused by gram-positive cocci, with gram-negative organisms and fungi being less frequently involved. However, two studies conducted in India found that a substantial proportion of POE cases (24.3% and 41.7%)

were caused by gram-negative organisms,[6,7] while fungi accounted for approximately 8% of cases.[8] Additionally, the administration of moxifloxacin as a prophylactic intra-cameral antibiotic has resulted in a rise in postoperative endophthalmitis (POE) caused by gram-negative organisms.[8]

The issue of antibiotic resistance is a significant concern currently. In the EVS study, gram-positive organisms were 100% susceptible to vancomycin. However, a review of endophthalmitis studies in PubMed between 1999 and 2015 found 27 cases caused by gram-positive organisms with reduced susceptibility or resistance to vancomycin.[9] A retrospective study[10] conducted in India found that 11.1% of culture-proven endophthalmitis cases were caused by gram-positive organisms resistant to vancomycin.

Regarding gram-negative organisms, the EVS study found that 89.5% were susceptible to amikacin and ceftazidime. In contrast, a study from India revealed that approximately 49% of gram-negative organisms were resistant to ceftazidime and 26% to amikacin.[11] The study concluded that multidrug-resistant POE is a matter of concern in India, and alternative antibiotics may be considered to manage resistant cases.

These findings raise the question of whether it's time to reconsider the empirical antibiotic combination recommended by EVS for the management of POE.

The evolution of MIVS

The EVS recommended core vitrectomy without induction of posterior vitreous detachment (PVD) in eyes presenting with visual acuity of light perception or worse. The reluctance for early vitrectomy in eyes with better vision was primarily due to the fear of iatrogenic breaks and retinal detachment. The advancement in vitrectomy technology,

now offers increased safety while operating in the proximity of the retina due to better fluidic control, adjustable cutting rates and variable port openings/duty cycle.[4] Additionally, wide field viewing systems have made PPV safer and more accessible. As a result, the threshold for PPV in the management of POE has decreased. In the past decade, several studies have shown that immediate pars plana vitrectomy (PPV) results in better outcomes and reduces the need for additional interventions. Also, the guidelines from the European Vitreo-Retinal Society (EVRS) recommended immediate PPV for managing postoperative endophthalmitis (POE), even in cases where visual acuity is better than perception of light (PL). Similarly, The EVRS Endophthalmitis Study Report 1, which examined the preferred practice pattern for managing POE and post-intravitreal endophthalmitis, noted that PPV was often performed regardless of the initial vision.[12] However, a meta-analysis of 15 case series revealed that vitreous tap and injection (TAI) was equally effective as PPV in treating post-cataract, post-intravitreal injection, and post-PPV endophthalmitis, though the specific inclusion criteria varied across the studies.

At our centre, we performed a small randomised controlled trial to study the effectiveness of immediate PPV versus TAI in patients with endophthalmitis after cataract surgery.[13] Our study included patients who presented with hand movement or better vision. Immediate PPV resulted in earlier recovery, lesser interventions, and a more significant change in visual acuity than TAI in eyes with PCE presenting with visual acuity of $\geq$HM. Although the final visual acuity was similar between the two primary groups, delaying PPV may adversely affect the outcomes. The most significant improvement was observed in patients with hand movement vision.

The current practice pattern favour early PPV; however, one needs to be aware that if

the facility for PPV is not available, intravitreal antibiotics before referral to a vitreoretinal centre significantly improves the outcomes and should be promptly given to all suspected patients of PCE.

Conclusion

Intravitreal antibiotics have been the cornerstone treatment for over 25 years in managing POE. However, with changes in microbial profile and antibiotic resistance, it may be necessary to change the empirical intravitreal antibiotics. A significant preference shift from EVS guidelines is the use of primary PPV, regardless of the presenting visual acuity.

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TIPS IN THE MANAGEMENT OF ENDOPHTHALMITIS WITH RETINAL DETACHMENT

Dr Arkaprava Pradhan

Medical Research Foundation,

Sankara nethralaya, Chennai

Dr Pramod S Bhende *

Medical Research Foundation,

Sankara nethralaya, Chennai

*Corresponding author

Introduction

Managing combination of retinal detachment (RD) and endophthalmitis remains a big challenge for retina surgeons. Concurrent endophthalmitis and RD may be seen in post-operative (8-10%),[1,2] post-trauma (6-37%),[3,4] and endogenous endophthalmitis (2-26%).[5, 6] The patient can present with RD and endophthalmitis or RD can occur at a later date during the course of management. The RD can be either rhegmatogenous (RRD), tractional (usually late onset) or exudative (due to severe inflammation), the commonest being RRD.

Concurrent endophthalmitis and RRD is relatively less common than the delayed-onset RRD in eyes with endophthalmitis.[7] Subsequent development of retinal detachment (RD) has been reported in up to 25% of eyes with endophthalmitis.[8]

Associated factors

In post-surgery settings, common factors associated with early (compared to delayed-onset) RD are infection with more virulent microorganisms (e.g. *S. aureus, Streptococci* or gram-negative bacteria), posterior capsular rupture, vitreous prolapse/ loss during cataract surgery, light perception vision at presentation and age ≥75 years.[1] The presence of posterior synechiae and aphakia are also reported to be associated with a higher risk of RD.[9] Aphakic eyes have a higher risk of retinal tears and RD, especially if there is associated posterior capsular rupture and vitreous loss during lens removal probably due to added traction on the retina.

Few patients may develop RD several weeks/months after completing antibacterial treatment or even after vitrectomy, suggesting that, chronic inflammation and/or vitreous traction may be involved in the pathophysiology of late retinal detachment in these eyes.[10] It has been reported that a systemic condition like diabetes, increases the likelihood of RD in exogenous endophthalmitis.[11]

In the setting of trauma, RD can be concurrent or delayed. Penetrating injuries can lead to full-thickness disruption of all layers of ocular tissues and also exposing the eye for potential infection. Delayed onset RD can be a late complication due to unrecognized / untreated traumatic retinal tear/s, iatrogenic retinal break/s induced during globe repair or during removal of intraocular foreign body. Additional risk factors associated with RD after trauma include a large posterior wound, choroidal hemorrhage, vitreous

haemorrhage,[3] infection due to more virulent organisms (e.g. *Bacillus* species, fungus) or due to poly-microbial infection.[12]

In eyes with endogenous endophthalmitis, incidence of RD is more with fungal infection (26%) than with bacterial (2%).[5,6] With endogenous fungal endophthalmitis, RD takes time to develop at least a week or more after the clinical diagnosis of endophthalmitis. Delayed onset RD after vitrectomy, usually occurs due to contraction of residual vitreous at sclerotomy sites or in the periphery, leading to new retinal break/s formation.[13]

Management options

To minimise the risk of proliferative vitreoretinopathy (PVR) and for better anatomical and functional outcome, RD repair needs to be planned at the earliest, in these eyes. However, in eyes with active infection, the primary goal is to control the infection. RD repair can either be planned at the same sitting or may needs to be delayed depending on the response to antimicrobials and severity of inflammation. Early vitrectomy is generally planned except in eyes with No PL vision, cloudy cornea (compromised visibility) and underlying severe inflammation.

A 4 or 6 mm infusion cannula is used to ensure safe infusion in vitreous cavity. A complete vitrectomy should be performed including PVD induction and thorough base excision, even though there is increased risk of iatrogenic break/s. Occasionally, one may need to perform relaxing peripheral retinectomy for adequate traction relief, especially in eyes with delayed RD. Subretinal fluid drainage can be performed through a pre-existing retinal break or drainage retinotomy. Endolaser photocoagulation is done around all the retinal breaks after fluid air exchange and anatomical retinal reattachment. Most often there is need for laser photocoagulation all along 360 degrees

in the periphery.

Silicone-oil is preferred as a long term internal tamponade in most of these eyes. Antimicrobial activity of silicone oil may also help in infection control.[14] Nagpal et al, in a randomized clinical trial, reported better anatomical outcomes and need for fewer subsequent surgical procedures in eyes which had silicone oil as an internal tamponade following vitrectomy.[15] Silicone oil may also help to stabilize or improve hypotony, which is frequently present in this setting. Silicone oil may also help in reducing the risk of recurrent RD, associated with PVR and may need to be left in place for prolong period in few patients.[15,16] Thomas BJ and his colleagues in their multicentre case series, reported significant improvement in final visual acuity following pars plana vitrectomy with silicone oil tamponade.[17]

In eyes with delayed-onset RD, after the initial treatment of endophthalmitis, intravitreal antimicrobials should be repeated, if there is suspicion of active infection. The normal intravitreal antibiotic dose needs to be modified in the silicone oil filled eyes. Systemic antimicrobials are always prescribed in post trauma and endogenous endophthalmitis setting. Usually scleral buckle is deferred due to potential risk of infection.

When corneal opacities obscure the view of vitreous cavity, the possible options would be to wait for corneal oedema to clear or to go ahead with temporary keratoprosthesis assisted vitrectomy followed by penetrating keratoplasty. Depending on the severity of the infection, extent of the RD and status of the cornea, the treating surgeon may take a call regarding appropriate timing for the surgery. There is a high incidence of graft rejection and quite a few of these eyes may need re-graft at a later date. Endoscope-assisted vitreoretinal surgery is an emerging technology and can be helpful in managing RD in these eyes with anterior segment opacities.[18]

Eyes with RD are considered 'inoperable', if there is 'no light perception' vision, phthisis bulbi, or anticipated very poor visual prognosis. In one of the large studies, 65.2% of endophthalmitis associated with RD were classified as 'inoperable'.[18] These eyes were managed with symptomatic treatment.

Treatment outcomes

Unlike in patients with primary, non-complex RRD, patients who develop RD with/ after endophthalmitis, generally have a poor visual prognosis. Two-thirds of these patients achieve best corrected visual acuity (BCVA) of 20/400 or less even after anatomical success.[7,19] In a subgroup analysis of the EVS, 78% eyes with delayed onset RD, could achieve anatomical success but only 38% of patients attained 20/40 or better vision.[1] In eyes with endophthalmitis and RD, other most common complications are recurrent RD with PVR and phthisis bulbi. 35% of eyes with concomitant RD and 30% of eyes with delayed-onset RD developed recurrent RD in a series reported by Dave et al.[7]

The most serious ocular sequelae of endophthalmitis is painful blind eye and the need for enucleation or evisceration. Wang et al, in their study, reported that, 8.7% of patients with 'endophthalmitis alone' underwent enucleation or evisceration but when the endophthalmitis was associated with RD, this rate was significantly higher i.e. 31.3%, confirming the inferior functional and anatomical outcome in eyes with RD secondary to endophthalmitis.[20]

Conclusions

1. Endophthalmitis associated RD is uncommon and generally has poor functional outcomes, even with early and appropriate management.

2. Endophthalmitis needs to be managed as per standard protocol.

3. Retinal detachment repair can be performed at the time of the initial management of endophthalmitis or at a later date depending on media clarity, severity of inflammation, complexity of the RD and expected visual prognosis.

4. Silicone-oil is a preferred internal tamponade.

5. Scleral buckle is generally avoided.

6. Virulence of the microorganisms is the most important predictive factor of visual and anatomical outcomes.

7. Despite timely intervention, almost one-third of the eyes with RD secondary to endophthalmitis, need enucleation or evisceration, highlighting the high incidence of poor anatomical and functional outcome.

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PERI-OPERATIVE PROPHYLAXIS FOR ENDOPHTHALMITIS

Dr. Divyansh Kailashchandra Mishra

Department of vitreo-retina and ocular oncology

Sankara eye hospital, Bangalore

Dr. Henal J Javeri

Department of vitreo-retina and ocular oncology

Sankara eye hospital, Bangalore

A number of possible sources of bacterial infection can be targeted for prevention. These include the tear film, eyelids, and adnexa of the eye; irrigating solutions and medications; surgical instruments, the respiratory and skin flora of the surgeon and assistants; and the operating room conditions. As, sterile surgical techniques can address many of these sources, infections are primarily believed to arise from the tear film, eyelids, and adnexa of the eye.[1] To avert endophthalmitis, essential steps include comprehensive preoperative assessment, minimising surface bacteria and preventing the growth of invading bacteria. Endophthalmitis prophylaxis is difficult to study because of its rarity and the many variables involved in ocular surgery.[2]

This article presents the best available evidence from literature, although it may not fully mirror the most effective clinical practices.

Cataract / Anterior Segment Surgery:

A. PREOPERATIVE PROPHYLAXIS:

1. Povidone iodine (PVI):

Povidone-iodine (PVI) is a broad-spectrum antimicrobial and bactericidal agent effective even against the drug-resistant bacteria. It works by releasing free iodine to the target cell surface.[3] It is the most effective method for preventing postoperative endophthalmitis.

European Society of Cataract and Refractive Surgeons (ESCRS) study,[4] a key guideline for endophthalmitis, recommends applying 5 % PVI to the cornea, conjunctiva, and periocular skin for at least 3 minutes before surgery. It can reduce ocular surface flora by 90%.[5]

Lower PVI concentrations (0.25–3.5%) have been explored. Dilute PVI (0.05–1%) reduces corneal toxicity.[3] However, conflicting results exist regarding the bactericidal effect of dilute PVI with no established guidelines.[3]

In the case of PVI allergy, aqueous chlorhexidine 0.05% can be an alternative.[4]

2. Preoperative antibiotics:

ESCRS guidelines have not established a clear benefit of preoperative fluoroquinolones along with PVI usage. It may, in fact, potentially increase the chances of bacterial resistance.[3] The United Kingdom Royal College of Ophthalmologists (RCOphth),[6] and

American Academy of Ophthalmology (AAO)[7] specifically do not recommend preoperative topical prophylactic antibiotics as well.

B. INTRAOPERATIVE PROPHYLAXIS:

Intracameral antibiotics:

The ESCRS study found that 1mg/0.1mL of intracameral cefuroxime injection at the end of surgery reduced endophthalmitis risk by fivefold.[4] The Endophthalmitis Study Report from rural India showed a 3.6-fold reduction in post-cataract surgery endophthalmitis, with no significant difference between intracameral cefuroxime and moxifloxacin (66.67% and 74.7% reduction, respectively).[8] Due to limited intracameral options, India prefers Moxifloxacin (15-100 mcg/0.1mL) and Vancomycin (100-500 mcg/0.1ml).[9]

A comparative meta-analysis has shown the lowest post operative endophthalmitis (POE) rate with Vancomycin.[9] However, occasional reports of associated hemorrhagic occlusive retinal vasculitis are concerning.[10] Moxifloxacin had a better safety profile with the second lowest rate of POE.[9]

C. POSTOPERATIVE PROPHYLAXIS:

ESCRS guidelines suggest postoperative antisepsis as per the surgeon's discretion, considering factors like the surgical environment, complications, and procedure-related risks.[4]

The Endophthalmitis Study Report 2 was a prospective comparative, non-randomized interventional Indian study.[11] They reported no statistically significant difference in endophthalmitis occurrence in patients without or with postoperative antibiotic

prophylaxis (any fluoroquinolone- Moxifloxacin/ Ciprofloxacin/Ofloxacin applied 4 times for 1 week) after having received intracameral moxifloxacin or vancomycin intraoperatively.

In 2017, the All-India Ophthalmological Society surveyed preferred antibiotic prophylaxis practices for intraocular surgery.[12] The Indian practice closely aligned with international guidelines, however only 83.8% routinely used PVI, and about 40% used intracameral antibiotics. The ground reality of clinical practice may not always be in accordance with the various guidelines and a nudge towards more evidence-based protocols would be beneficial.

Posterior Segment

A. Intravitreal injections:

Intravitreal injections (IVI) have become the main treatment modality for several common ocular conditions. Its efficacy has made it the most performed procedure in ophthalmology.[13] Topical antibiotics were initially used before and after IVI to reduce the risk of post-IVI endophthalmitis. However, repeated use of topical antibiotics can increase antibiotic resistance of ocular surface flora, increasing infection risk.[14,15,16]

The Comparison of AMD Treatments Trials (CATT) suggested that the post-injection endophthalmitis rate was low and similar to those in other large-scale studies. Use of peri-operative topical antibiotics did not appear to reduce the risk for endophthalmitis.[17]

The recent guidelines of the American Academy of Ophthalmology[18,19] and several systematic reviews have also had a similar conclusion.[20,21] Strict rules of asepsis remain the only evidence-based prophylaxis.

Vitreo-Retina Society of India - Guidelines for intra vitreal injections[22]

Peri Operative

- Screen for infection, blocked nasolacrimal duct. Treat active infection before injection. Treat uncontrolled systemic conditions.
- Time-out before injection. Bilateral injections not recommended.
- Preoperative topical antibiotics may be helpful.
- Intravitreal injection should be performed in an operating room or a sterile room.
- Use 10% povidone-iodine to clean the skin and periocular adnexa, and 5% povidone-iodine drops in the conjunctival sac for 3 minutes. Instill one drop of proparacaine eye drops before instilling povidone-iodine drops.
- Drape the surgical area using sterile linen and a separate plastic sticking eye-drape for each patient. Use a sterile speculum to prevent contact of the eyelashes and eyelid margins with the injection site and needle.
- Inject under an operating microscope. Any quadrant can be chosen for injection.
- Post-injection, the cul de sac needs to to be flushed with povidone iodine or the injection site dabbed with a povidone iodine soaked sterile swab. The eye can be patched with povidone iodine 5% drops for 2 hours after injection.

Post Operative

- Post-injection antibiotic use is left to the discretion of the ophthalmologist.
- Maintain proper lid hygiene. Monitor IOP and use anti-glaucoma drugs if needed.
- Give a discharge card with injection details, symptoms of infection, and emergency contact info.

- Avoid washing eyes for 24 hours.
- Tailor follow-up to indication for injection.

Although some experts have theorised that topical PVI and antibiotics could have a synergistic effect in reducing conjunctival flora, a randomised controlled trial (RCT) did not find any additional benefit of the combination.[23]

Antimicrobial stewardship and proper antimicrobial usage minimises resistance development. It is important to choose wisely. Preoperative antibiotics are not necessary for routine uncomplicated surgery. However, it may be considered in monocular patients, those prone to infection, having a poor tear film or were immuno-compromised.[24,25,26,27]

Medico Legal Standpoint- Adhering to the community norm is a safer approach, even if it's not the optimal practice as no unanimous strategy exists for preventing endophthalmitis post intravitreal injections. Ultimately, deciding on antibiotic use post-injection is complex, requiring a case-specific evaluation of the risk and benefit.[28]

B. Vitrectomy Surgery

In the 1970s, subconjunctival antibiotics were routinely used in PPV surgery, as they were considered the standard of care for all intraocular surgeries. However, a study published in RETINA found that the rate of post-operative endophthalmitis was not statistically different between patients who received subconjunctival antibiotics (0.078%) and those who did not (0.10%). The study included 18,886 patients.[29] Antibiotics like other medications have risks, benefits, and costs.[30]

A Microsurgical Task Force addressed these concerns with evidence-based recommendations.[31]

- PVI- 5% in conjunctival sac
- Proper draping- lashes out of surgical field
- Conjunctival displacement during port making
- Angled scleral incisions
- Minimising vitreous incarceration-
- Wound inspection—suture placement
- Tamponade to prevent hypotony.
- Postoperative subconjunctival and topical antibiotics can be used while avoiding retinotoxic antibiotics such as gentamicin.

Muna Bhende et al. conducted a retrospective study evaluating incidence of endophthalmitis before and after introducing preoperative povidone-iodine drops for vitrectomy patients. Pre-2000, patients were given preoperative antibiotics for at least 3 days, alongside 0.5% cetrimide solution cleaning prior to surgery. Post-2000, patients had antibiotics for one day before surgery, 5% PVI drops in the conjunctival sac for 3 minutes and periocular cleaning with 1% povidone-iodine solution. They found no significant difference in the incidence rates.[32]

A multicentric study published by VRSI study group[33] in India revealed that irrespective of the type of prophylaxis at the end of surgery (topical antibiotic alone/ povidone iodine alone/ a combination of both / subconjunctival alone / topical and subconjunctival antibiotics), no significant difference in the endophthalmitis rates was noted with different preoperative and postoperative antibiotic prophylaxis.

C. Scleral buckling

A study of 2,972 scleral buckling procedures found that soaking the buckle in antibiotics during surgery significantly reduced the risk of infection or extrusion. However, a more recent study of 1,127 procedures found that soaking the buckle in antibiotics did not affect the risk of infection or extrusion.[34,35]

AIOS Task Force guidelines:

Keeping the Indian scenario in mind, the All India Ophthalmological Society Task Force has laid down guidelines for endophthalmitis prophylaxis for intravitreal injections.[36]

- Apply 5% povidone-iodine to the conjunctival sac for 3 minutes or until dry.
- Preoperative antibiotics are preferable, but not mandatory.
- Subconjunctival antibiotics are not necessary.
- Topical broad-spectrum antibiotic drops can be instilled.
- Intracameral antibiotic use is at the discretion of the surgeon. Moxifloxacin (100-500 micrograms/ 0.1 ml) or cefuroxime 1 milligram/0.1 ml should be preferred if used.
- Postoperative topical antibiotics for 7-10 days are optional.

In Conclusion -

1. **Preoperative Prophylaxis:** Applying 5 % PVI to the cornea, conjunctiva, and periocular skin for at least 3 minutes before surgery has shown the most benefit universally.
2. **Intraoperative Prophylaxis** - Intracameral options include Cefuroxime (1mg/0.1 ml) Moxifloxacin (15-100 mcg/0.1mL) and Vancomycin (100-500 mcg/0.1ml). intraoperative prophylaxis can be used for posterior segment only if required.
3. **Postoperative antibiotic prophylaxis** is as per the surgeon's discretion.
4. **For Intravitreal Injections** - The prophylaxis needs to be chosen wisely.

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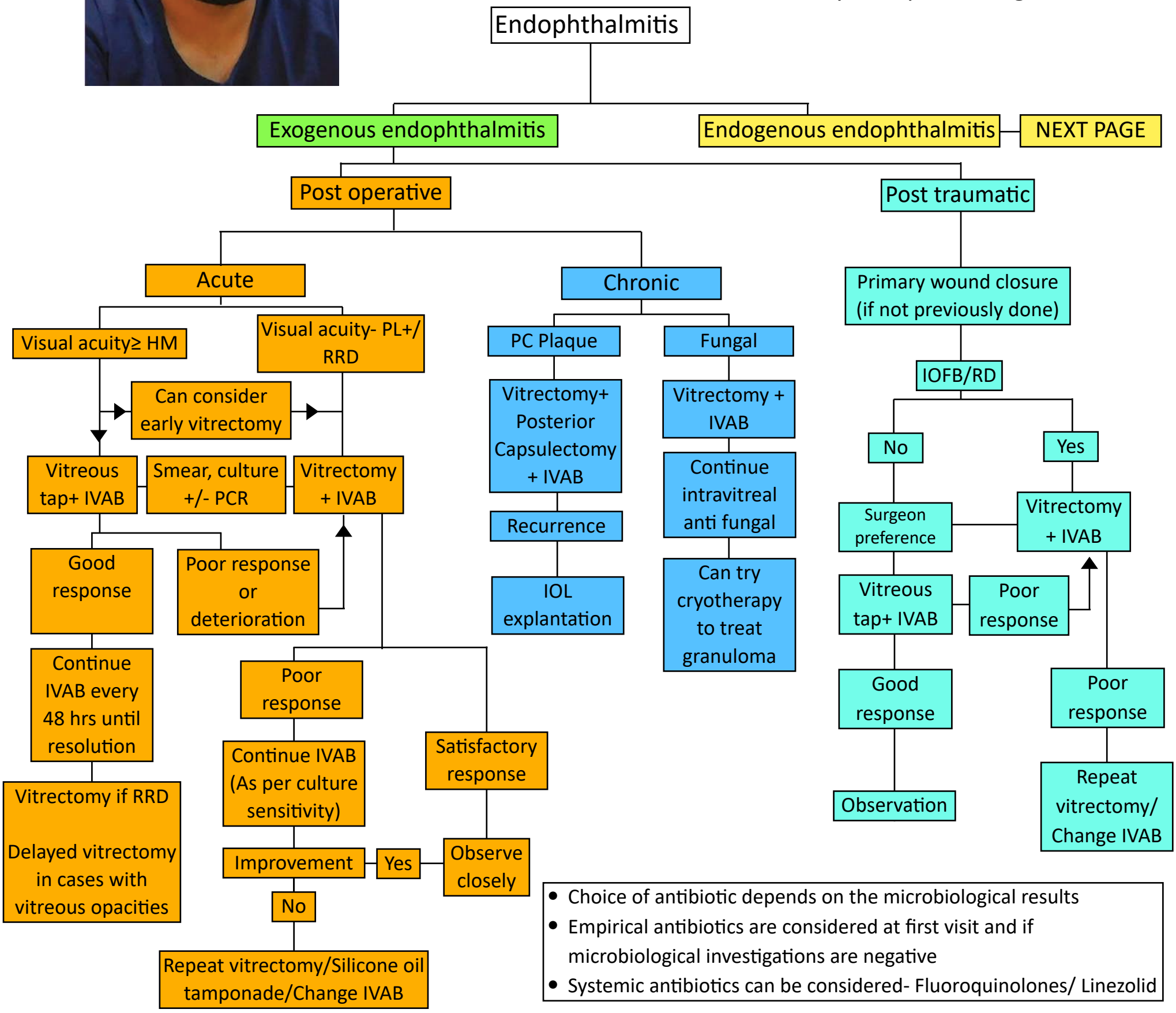
MANAGEMENT OF ENDOPHTHALMITIS IN A SCHEMATIC

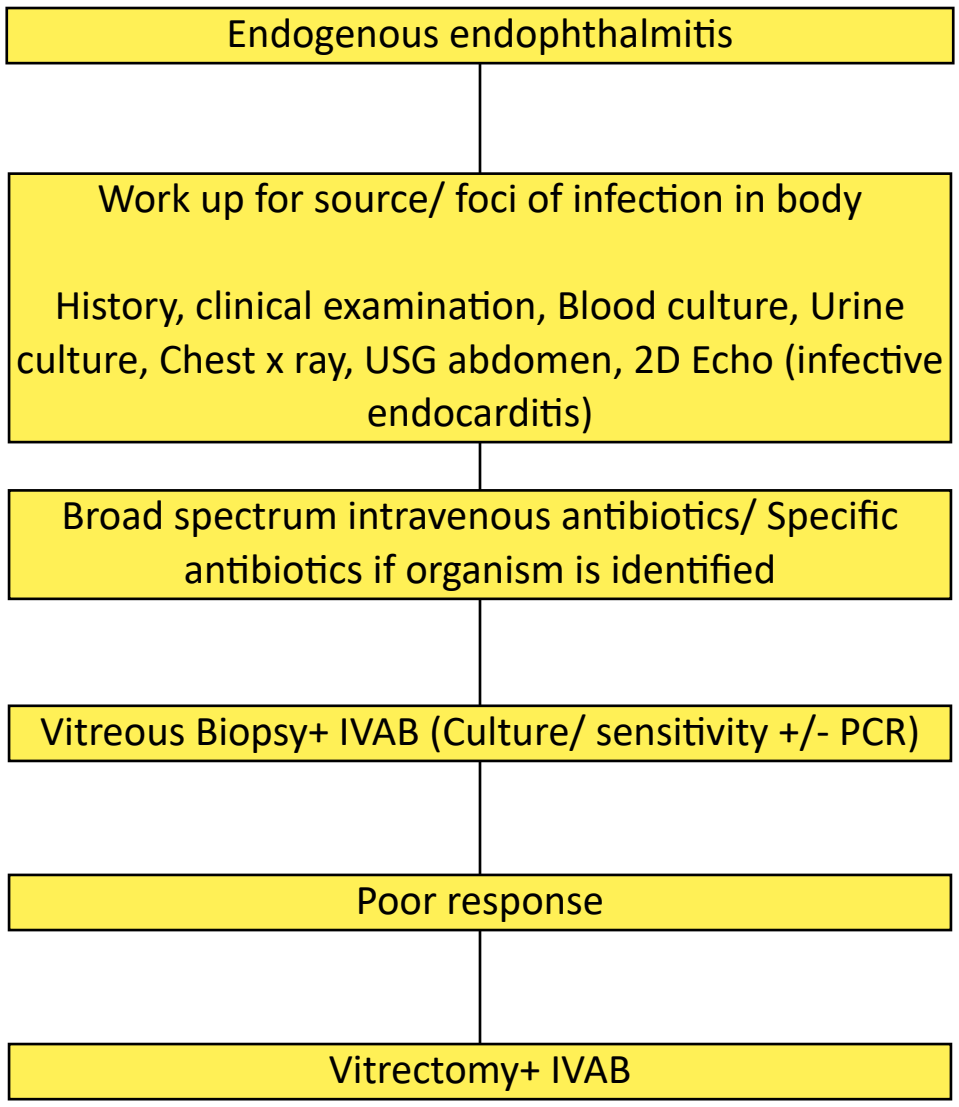
Dr. Devashish Dubey

Consultant- Vitreo retina, ROP and Uvea services
ASG-Vasan eye hospital, Bengaluru



- Choice of antibiotic depends on the microbiological results
- Empirical antibiotics are considered at first visit and if microbiological investigations are negative
- Systemic antibiotics can be considered- Fluoroquinolones/ Linezolid

MANAGEMENT OF ENDOPHTHALMITIS IN A SCHEMATIC

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