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Endophthalmitis Management: Stain-Culture, Empirical Treatment, and Beyond

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The current standard of care for endophthalmitis is greatly influenced by a large prospective randomized study in the United States—the Endophthalmitis Vitrectomy Study (EVS).[1] This study proposed three management principles: (1) microbiological evaluation of intraocular fluid (vitreous; and if not, at least anterior chamber fluid) in all cases; (2) intravitreal antibacterial antibiotics (ceftazidime and vancomycin) empirically in all eyes; and (3) presenting vision-based primary surgical intervention (vitreous tap for presenting vision of hand motions or more, and vitrectomy for presenting vision of light perception or less). This study was confined to acute post-cataract and post-secondary intraocular lens surgery endophthalmitis, though many treating ophthalmologists extend the same management strategy to other causes of endophthalmitis. The decision to employ the EVS treatment recommendations decades after the study is questioned,[2,3] though two EVS suggestions—microbiological evaluation of intraocular fluid and intravitreal antibacterial antibiotics injection—have stood the test of time.

The spectrum of infecting organisms and the antimicrobial susceptibility is not same the world over. Two large prospective randomized studies, the EVS[1] and the European Society of Cataract and Refractive Surgeons (ESCRS) study,[4] did not include cases where fungal infection was suspected. Fungal endophthalmitis is uncommon in Europe and infrequently reported from North America,[5,6] but not in the Asia Pacific region where it could account up to 20% of acute post-cataract surgery endophthalmitis.[7–9] Gram-negative infection was also very small in these randomized trials,[1,4] whereas it accounts up to 26% in Asian countries.[7–9] Visual outcome of fungal endophthalmitis is poor[10,11]; infection secondary to molds has a worse outcome than those due to yeasts[12] and the visual outcome of *Aspergillus* endophthalmitis is invariably poor because of the preferred macular involvement by this fungus.[13] The outcome of endophthalmitis caused by gram-negative infection is also poor, it is particularly worse in *Pseudomonas aeruginosa* infection.[1,14,15] The EVS recommended intravitreal ceftazidime for gram-negative infection. Ceftazidime is a beta-lactam third-generation cephalosporin, it affects the bacterial cell wall synthesis by inhibiting peptide cross-linking of polysaccharide chains of peptidoglycans. It causes filamentation and eventually cell lysis of *P. aeruginosa*.[16] In our study in India, ceftazidime susceptibility of gram-negative bacteria was around 61%[17] as against 89% in the EVS[1]; it is decreasing over last 25 years.[18,19] We have documented variable susceptibility of gram-negative bacteria from different locations in patients that developed postoperative endophthalmitis in our institution and those referred from elsewhere for endophthalmitis management.[20] We reported poor outcome of gram-negative endophthalmitis, that many micro-organisms were resistant to ceftazidime, and a third of the eyes resulted in phthisis.[21]

There are two publications on endophthalmitis in this issue of the journal. The article from New Zealand discusses the factors that yield positive microbial culture.[22] The authors suggest culturing both aqueous and vitreous fluid. They have identified three factors that impact positive culture: vitreous collected at the beginning of vitrectomy (odds ratio, OR 2.86), eyes presenting with absent red reflex (severely infected eyes, OR 2.73), and anterior chamber fluid collected by aqueous tap (OR 2.06). The culture positivity was 32.1% for the anterior chamber fluid and 45.3% for vitreous fluid. The culture positivity in this study was at least 20% lower than that reported in the EVS (69.3%) and ESCRS study (68.9%).[1,4]

There are many reasons for reduction of culture positivity. Over diagnosis is one of them; equally important ones are small sample size, sequestration of microorganisms in the capsular bag, prior antibiotic therapy, and delay in processing the samples. These difficulties are overcome by the newer methods of molecular microbiology. The classical molecular microbiology method is the polymerase chain reaction (PCR) and its variants such as the real-time PCR (RT-PCR) or quantitative PCR (qPCR). PCR reaction is highly specific and sensitive.[23] Panbacterial or eubacterial PCR using 16S rDNA gene primers has been extensively used for the diagnosis of bacterial endophthalmitis.[24–26] RT-PCR for bacterial endophthalmitis has been described using universal bacterial probe, gram-positive probe, and several bacterial genus-specific probes.[27] More recent molecular microbiological diagnostic method in endophthalmitis is the next-generation sequencing.[28–30] Attempts are also made to use biomarkers to confirm the infectious endophthalmitis.[31,32]

From the L V Prasad Eye Institute, Hyderabad, India.
Submitted October 20, 2019; accepted December 5, 2019.
The authors have no funding or conflicts of interest to disclose.
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ISSN: 2162-0989
DOI: 10.1097/01.APO.0000617904.11979.ae

An article from India has documented the clinical characteristics of a large series of endophthalmitis caused by *Aspergillus* species and has analyzed the factors that impact the visual outcome.[33] The authors stated that nearly half of the cases occurred after trauma; better functional outcome (defined as an attached retina and vision ≥20/400) was obtained when there was no corneal infiltrate on presentation (OR 5.40), vitreous surgery was the primary procedure (OR 4.26), intravitreal voriconazole (OR 3.63) injection was given, and the presenting vision was Hand motions or better (OR 3.33).

Two large series of fungal endophthalmitis have been published from India in the last decade.[34,35] In these reports, infection with filamentous fungi was higher and *Aspergillus* species was the most common infecting fungus. The outcome, anatomical and functional, in these combined 177 eyes was suboptimal. To improve the outcome, an early vitrectomy with or without intraocular lens explanation and intravitreal antifungal antibiotic injection were suggested.[35,36] Explantation of intraocular lens (IOL) is advocated in delayed-onset infection, including fungal endophthalmitis. One published report indicates faster resolution of inflammation and reduced number of intravitreal injection when the IOL is explanted in chronic endophthalmitis.[37]

Unlike a repertoire of antibiotics in bacterial infection, the choice of antifungal antibiotic for intravitreal injection is currently confined to only two antibiotics: amphotericin B and voriconazole. Amphotericin B is a polyene antibiotic; it binds to ergosterol to alter the permeability of cell wall. Half-life ($t_{1/2}$) in vitreous of noninflamed phakic eyes is 8.9 days, and in aphakic vitrectomized eye it is only 1.8 hours. Yeasts and filamentous fungi are susceptible to amphotericin B, but many species of *Aspergillus* are resistant. Voriconazole is a triazole compound; it inhibits ergosterol synthesis, which increases membrane permeability. Half-life of voriconazole in vitreous of noninflamed phakic eyes is 2.5–6.5 hours; it has broad-spectrum activity against molds and yeasts.[38] Bioavailability after systemic treatment is better with voriconazole than amphotericin B. However, voriconazole is a known hepatotoxic and amphotericin B is a known renal toxic.[39]

The EVS recommendation for vitrectomy was based on the presenting vision: primary vitrectomy only for eyes with vision of light perception or less and vitreous tap in all other eyes.[1] Despite some contests,[2,3] this strategy holds true in care of post-cataract surgery acute bacterial endophthalmitis, but it does not extend to other forms of endophthalmitis. Vitrectomy and intravitreal antibiotic must be the primary treatment in all delayed-onset and chronic (many times fungal) endophthalmitis. The question is how much of vitrectomy should one perform in eyes that are infected and the retina vulnerable to vitreous surgery–induced manipulations. The EVS recommended only a core, not a complete, vitrectomy.[1] This again may not be enough to achieve good functional result in many instances of chronic endophthalmitis and endophthalmitis after trauma. To repair the iatrogenic retinal damage, these eyes could require a midterm tamponade such as with silicone oil.[40,41] In addition to exerting endotamponade, silicone oil could also exert its inherent antimicrobial effect.[42]

One of the advantages of routine microbiology study in endophthalmitis is estimating the minimum inhibitory concentration (MIC, defined as the lowest concentration of an antimicrobial agent that prevents visible growth of microorganisms) of the antibiotic. MICs are used to evaluate the antimicrobial efficacy of various compounds by measuring the effect of decreasing concentrations of antibiotic inhibiting microbial population growth over a defined period.[43] MICs that confirm resistance of bacterial species are performed routinely in many laboratories. MIC is not routinely performed for antifungal antibiotics. But MIC of antifungal antibiotics is required for the similar reasons that the antibacterial antibiotics MIC is performed: increasing number of people with profound immunosuppression and the possibilities of invasive fungal infection; development of new antifungal drugs; and the emergence and recognition of antifungal resistance. MIC breakpoints are available for amphotericin B, fluconazole, itraconazole, voriconazole, and flucytosine against *Candida* and some species of filamentous fungi.[44] It is not available for all species of filamentous fungi. One of the major deficiencies of the susceptibility testing including the MIC is the in vitro-in vivo correlation. One is equally unsure if the minimum fungicidal concentration (MFC, defined as the lowest concentration of the drug that achieves ≥98–99.9% killing of a particular fungus) correlates better with the clinical outcome.

These two articles in this issue[22,33] raise some important questions: (1) Should one continue to identify the infecting microorganisms in view of the current recommendations of empirical selection of intravitreal antibiotics? (2) Should one continue to depend on classic stain and culture methods? (3) Should not one consider including intravitreal antifungal antibiotic in combination with the antibacterial antibiotics in primary care of endophthalmitis in the regions of the world where fungal infection is not uncommon? The answers, in short, could probably be "yes" for continuing detection of infecting organisms but with newer molecular techniques, for susceptibility testing with greater emphasis on MIC and MFC, and for region-specific different combination of intravitreal antibiotics.

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