Management of cluster endophthalmitis does not stop at clinical care

Cluster endophthalmitis is the occurrence of endophthalmitis much higher than the local incidence pattern or occurrence of two or more cases of infection at a time, or the occurrence of repeated postoperativee infection under similar circumstances— with the same surgeon, same staff, or in the same operating room. This calls for many interlinked actions and responsibilities on the service provider. These essentially include (1) to treat the patients most appropriately to salvage the best possible vision, (2) identify the source of infection to prevent another outbreak, and (3) build the psychosocial confidence in both the caregivers and the care seekers.

Treatment of the infected eyes is on the similar lines of the endophthalmitis vitrectomy study (EVS) recommended standard of care,[1] but more often vitrectomy than vitreous tap is required, and culture-susceptibility specific (as opposed to empiric) intraocular antibiotics benefit the patients. The outcome depends on the speed of instituting treatment, the possibilities of doing a good vitrectomy, and the susceptibility of the infecting microorganism. A good vitrectomy is possible when the cornea is not grossly affected and the causative organisms are not multidrug resistant (MDR).

There are three sources of infection after an intraocular surgery— the patient, the health personnel, and the surgical supply. Potential sources of these outbreaks usually include bacterial contamination from the surgical instruments, irrigating fluids, intraocular lens, or the surgical environment. Isolated cases of acute postoperative endophthalmitis usually arise from the patient's own commensal bacteria and these are mainly gram-positivee cocci. In contrast, gram-negative organisms are commonly associated with epidemics of cluster endophthalmitis outbreaks after cataract surgery. *Pseudomonas aeruginosa* is more often reported gram-negative microorganisms in cluster endophthalmitis from India.[2-4] Molecular microbiological methods are essential to prove an unquestionable association of the microorganism isolated from the vitreous of the infected eye and other suspected sources of infection, be it the surgical supply or the healthcare personnel.[5,6] The functional success (defined as best-corrected final visual acuity ≥ 20/200) in 101 cases of reported cluster *Pseudomonas aeruginosa* endophthalmitis in India in the recent past including the one reported in this issue of the journal is under 25% [Table 1].[2-4,7] Worse is the outcome when the cornea is involved (does not allow good vitrectomy) and the infecting organism is MDR. Between the two, MDR is the greater evil.

MDR is insensitivity or resistance of a microorganism to the administered antimicrobials despite earlier sensitivity to it. MDR could be primary (the microorganism has never encountered the drug of interest), secondary (acquired resistance that arises after exposure to the drug), or clinical (the drug concentration is insufficient to impact the microorganism).[8] A large study spanning 25 years and an analysis of over 3300 culture-positive cases of infective endophthalmitis in India have reported an increase in the resistance of gram-negative organism to ceftazidime from 31% in 2005 to 62% in 2015.[9] Another study from the same center in India has shown that all 56 MDR gram-negative organism (59% of them were *Pseudomonas aeruginosa*) were 100% susceptible to imipenem and only partially susceptible to amikacin, ciprofloxacin, and gentamicin (43%, 41%, and 30%, respectively)[10] Resistance to ceftazidime has been recorded by the EVS group in the USA (11%),[1] and this has been confirmed in reports from India (up to 40%).[11-13] In addition to imipenem, colistin and piperacillin are considered good alternatives to treat MDR *Pseudomonas* spp. In the current report from Central India, susceptibility of *Pseudomonas aeruginosa* to colistin, piperacillin, and imipenem was 82%, 68%, and 64%, respectively by disc diffusion method.[6] [The Clinical and Laboratory Standrad Institute, CLSI, guidelines do not recommend testing of colistin and imipenem by disk diffusion method].

Colistin is a multicomponent polypeptide antibiotic that is mainly composed of colistin A and colistin B. It is available as colistin sulfate (tablets or syrup for oral use and powder for topical use), and colistin methanesulfonate (colistimethate sodium [CMS]). Colistin binds to the lipopolysaccharides and phospholipids in the outer cell membrane of gram-negative bacteria and disrupts the outer cell membrane.[14]

Imipenem is a β-lactam antibiotic highly resistant to the β-lactamase enzymes produced by many MDR gram-negative bacteria, particularly *Pseudomonas aeruginosa* and *Enterococcus* species. Imipenem inhibits cell wall synthesis by binding to penicillin-binding proteins.[15] Piperacillin/tazobactam is a combination medicine containing antibiotics, piperacillin and β-lactamase inhibitor, tazobactam. The combination has activity against many gram-positive and gram-negative bacteria including *Pseudomonas aeruginosa*. Tazobactam inhibits

Table 1: Cluster endophthalmitis caused by *Pseudomonas aeruginosa* in India[2-4,7]

Reporting Year/ City	*n*	Occurrence	Median time to treatment	Antibiotic Resistance	Final VA ≥20/200
2009 Tiruchirapalli[2]	20	In-house	5.5 days	Partial: Cipro (75%), Moxi (80%)) Total: Ami, Chlor, Gati	0/20
2011 Hyderabad[3]	11	In-house	1 day	Total: Cefur, Chlor	9/11 (81.8%)
2014 Mumbai[4]	8	Referred	2 days	Total resistance to all antibiotics except Colistin	7/8 (87.5%)
2020 Raipur[7]	62	Referred	5 days	Partial: Ami (67.5%); Chlor (75%); Cipro (89.4%); Gati (92.5%); Imi (36%) Total: Moxi	9/62 (14.5%)

Ami=Amikacin, Cefta=Ceftazidime, Cefur=cefuroxime, Chlor=Chloromphenicol, Cipro=ciprofloxacin, Gati=gatifloxacin, Imi=imipenem, Moxi=moxifloxacin

Table 2: Antibiotics for multidrug-resistant gram-negative bacterial endophthalmitis

Antibiotic	Intravitreal	Topical	Systemic
Colistin 1 million IU (75 mg)	Add 10 ml NS Take 0.1 ml + 0.9 ml NS ml=1000 IU (double dilution)	10 mg/ml Add 10 ml DW Take 1 ml + 3 ml DW	1 million IU twice daily
Imipenem 500 mg	Add 10 ml NS Take 0.1 ml + 0.9 ml NS ml=50 µg (double dilution)	1 mg/ml Add 10 ml DW Take 1 ml + 4 ml DW (store in amber colored bottle)	1 g twice daily
Piperacillin & Tazobactam 4.5 mg	Add 20 ml NS Take 0.1 ml + 0.9 ml NS ml=225 µg (double dilution)	-	-

DW=Distilled water, N.S=Normal saline

β-lactamase and prevents the destruction of piperacillin. Piperacillin kills bacteria by inhibiting the synthesis of bacterial cell walls. It binds to specific penicillin-binding proteins (PBPs) located inside bacterial cell walls.[16] Table 2 lists the dosage for ophthalmic and systemic therapy of these drugs.

Culture of the ocular fluid (vitreous or aqueous) and the intraocular lens, if extracted, and antibiotic susceptibility testing of the culture isolates is essential to effectively treat cluster endophthalmitis. This is traditionally performed by inoculating the material in a number of culture media and grow them both aerobically and anaerobically. The species identification is done by the traditional biochemical tests or automated Vitek 2 system. But the responsibility of the care provider does not stop with this. Every effort must be made to identify the source of cluster infection by subjecting to similar microbiological tests of materials collected from all possible sources, such as the surgical instrument and supply, and the environment including the air conditioning ducts. However, these methods do not establish a cause-effect relationship with certainty unless the offending organism from the patient and suspected source are proven to be identical by molecular method. The methods used in many centers investigating cluster endophthalmitis include polymerase chain reaction with enterobacterial repetitive intergenic consensus (ERIC- PCR),[2,3] high sequence genotyping,[5] random amplification of polymorphic DNA (RAPD) assay,[6] and pulsed-field gel electrophoreses of the organism (*Pseudomonas aeruginosa*).[17] These molecular tests unequivocally establish the source of infection so that one could institute appropriate measures to prevent a recurrence. This is the most crucial inquiry in every outbreak of cluster endophthalmitis.

The Royal College of Ophthalmology, UK provides a very comprehensive guideline for managing the outbreak of postoperative endophthalmitis.[18] It recommends constituting a team that includes physicians, microbiologists, and operating room nurses. The team collects a comprehensive list of notes from the medical records and investigates the operating room, pre- and postoperative areas, central stores, and sterilization areas. Depending on the number of cases, a color-coded alert is made as follows[18]:

Green- 1 case of endophthalmitis; 1 in ≥100 cases, or 2 in ≥600 cases;

Amber- 1 case in 75 cases, 2 cases in 300-500 cases, 3 cases in 700-800 cases;

Red- 2 cases in ≤200 cases, 3 cases in ≤600 cases, 4 cases in ≤ 800 cases.

A 'green alert' calls for heightened vigilance, but an 'amber' or 'red alert' may necessitate the closure of operating rooms to investigate for the cause of the outbreak.

Finally, the psychosocial aspect of care cannot be ignored. In an environment of mental and physical trauma to the patient and family, to the operating physician and the eye care facility, one is required to maintain a dignified calm, and use an alert and logical mind to tide over the crisis of restoring confidence to everyone involved with the incident. The report in this issue dealing with six clusters of *Pseudomonas* endophthalmitis is from the same region that had encountered similar incidents a few years ago.[19] On both occasions, appropriate care had been provided though vision in many eyes could not be saved due to late presentation, advanced disease status, and virulent organisms. But a proper investigation was not done to identify the cause. A national policy should be made where reporting such outbreaks and a thorough inquiry are made mandatory.

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