OCULAR INFECTIONS
Prophylaxis and Management

Salient Features

- An explicit and easy-to-read book
- Provides comprehensive information on operation theatre design, layout and requirements for setting up an operation theatre
- Highlights the methods of sterilization and disinfection of operation theatre and instruments with special reference to ophthalmic operation theatre
- Enlists the prophylactic measures to be taken pre-, intra- and post-operatively for the prevention of post-surgical infections of the eye
- Provides step-by-step management protocols for the timely and proper treatment of post-operative ocular infections
- Includes original good quality photographs wherever appropriate for a simplified understanding of the text
- The chapters are supplemented with flow charts and tables for easy comprehension of the subject
- Useful for the whole ophthalmic team: the surgeons, nursing staff, ophthalmic assistants and postgraduate students.

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Includes
- Operation Theatre Design
- Sterilization and Disinfection of OT and Instruments
- Post-Surgical Ocular Infections

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Dedicated to
My parents, Dr Ramesh C Sharma and Mrs Maitreyi Pushpa,
husband Dr Subhash Chandra and daughter Vasavadatta
—Namrata Sharma

My parents, Mr Rakesh Aron and Mrs Anshu Aron and
husband Dr Kanav Kaushal
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My late parents, Mr Sanat Kumar and Mrs Swarna Kumar,
wife Mrs Parul Kumar and children Aman and Aarshi
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Post-surgical ocular infections are serious vision-threatening complications of any intra- or extraocular surgery which are avoidable. The infections vary in terms of time of onset, severity and course. They may range from a small infiltrate to the most serious of these complications such as post-operative endophthalmitis or panophthalmitis leading to loss of the eye. We, as ophthalmic surgeons, have the major responsibility of taking all measures to reduce this risk to a minimum. The onus is on us to bring down the incidence of post-operative infections and achieve successful visual outcomes. Various books on management of infections in ophthalmic practices are available; however, none provides in detail the basic precautions to be followed and steps to be taken pre-operatively, intra-operatively and post-operatively to prevent the occurrence of ophthalmic infections. With the rising number of dedicated centres for ophthalmic practice both in the government and private sector and increase in the number of ocular surgeries being performed, the incidence of infection and endophthalmitis is on a rise which is a dreaded complication and a nightmare for ophthalmologists. This calls for a certain set of criterion to be followed at every step to prevent such avertable complications. This book attempts to lay down guidelines for the prophylaxis of ocular infections which must be followed and are useful not only for the ophthalmic surgeons but also for the nursing staff, ophthalmic assistants and postgraduate students. The first half of the book enlists the prophylactic measures to be taken to prevent post-operative infections. The second part of the book deals with the management of cases of infection after various ophthalmic surgeries when they occur, despite taking all precautions. The book has been written in a user-friendly style with a precise format assisted by suitable illustrations and tables, wherever appropriate for easy understanding. We hope that the book will serve its purpose of providing useful guidelines to the ophthalmic community to prevent post-surgical ocular infections and reduce ocular morbidity.

Namrata Sharma
Neelima Aron
Atul Kumar
## Contents

1. **Introduction**  
   *Nishat Hussain Ahmed, Gita Satpathy*  
   - History 1  
   - Cleaning, Disinfection and Sterilization 2  
   - Cleaning 4  
   - Sterilization and Disinfection 5  

2. **Operation Theatre: Design and Layout**  
   *Ritika Mukhija, Neelima Aron, Namrata Sharma, Atul Kumar*  
   - History 15  
   - Setting up an Operation Theatre 15  
   - Layout 16  
   - Lighting 19  
   - Temperature and Humidity 19  
   - Scrub Room 19  
   - Recovery Room 19  
   - Minor Operation Theatre 20  

3. **Air Flow System in Ophthalmic Operation Theatre**  
   *Prateek Kakkar, Neelima Aron, Atul Kumar*  
   - Ventilation/Air Conditioning 22  
   - Laminar Air Flow 23  
   - Air Change Per Hour 23  
   - Air Velocity 23  
   - Positive Pressure 24  
   - Air Filtration 24  
   - Maintenance of Air Flow System 24  

4. **Water Requirement in Ophthalmic Operation Theatre**  
   *Mrittika Sen, Neelima Aron, Namrata Sharma, Atul Kumar*  
   - Handwashing 26  
   - Instruments 26  

5. **Operation Theatre List and Record Maintenance**  
   *Pranita Sahay, Srikant Kumar Padhy, Neelima Aron*  
   - The Operation Theatre List 29  
   - Recommendations 29  
   - Special Considerations while Preparing an Operation Theatre List 30  
   - Distribution of the Operation Theatre List 31  
   - Record Maintenance in Operation Theatre 31
6. **Pre-operative Patient Preparation**  
*Mukesh Patil, Neelima Aron, Namrata Sharma, Atul Kumar*  
- Pre-operative Measures 33  
- Operation Theatre Attire 34  
- Marking and Cleaning of the Surgical Area 34  
- Shifting the Patient to Operation Theatre 35  
- Surgical Preparation 35  
- High Risk: HIV, HBsAg, HCV 36

7. **Pre-operative Preparation of Operation Theatre Personnel**  
*Archita Singh, Sagnik Sen, Ankit Singh Tomar, Neelima Aron*  
- Operation Theatre Occupancy 38  
- Operation Theatre Attire 38  
- Components of the Attire 39  
- Special Cases: HIV, Hepatitis B and C 41  
- Surgical Scrubbing 42  
- Gowning and Gloving 43

8. **OT Protocol: Codes of Conduct**  
*Sagnik Sen, Neelima Aron, Vaishali, Namrata Sharma*  
- General Considerations 47  
- Scrubbed Surgeon and Assistant 47  
- Nursing Staff 48  
- Operation Theatre Assistant 49  
- Observer in the Operation Theatre 50  
- Visitors in the Operation Theatre 50  
- Intra-operative and Post-operative Practices 50  
- Practices in the use of Intra-operative Adjuncts 51

9. **Operation Theatre Sterilization**  
*Ruchita Falera, Sagnik Sen, Neelima Aron*  
- Operation Theatre Cleaning 52  
- Operation Theatre Disinfection and Sterilization 53  
- Cleaning Schedule 55  
- Septic Operation Theatre 55  
- Special Cases: HIV, Hepatitis B, Hepatitis C 56

10. **Ophthalmic Instrument Sterilization**  
*Nishat Hussain Ahmed, Manthan Chaniyara, Sagnik Sen, Neelima Aron, Gita Satpathy*  
- Instrument Processing 57  
- Sterilization 59  
- Instrument Sterilization in Ophthalmic OT 64

11. **Waste Disposal in Ophthalmic Operation Theatre**  
*Reena Singh, Rajesh Sinha*  
- Categorization of Waste in Operation Theatre 69  
- Segregation and Accumulation of Categorized Waste 69  
- Packaging of Segregated Wastes 70  
- Transportation of Packed Wastes from OT to Final Site of Treatment or Disposal 71  
- Treatment of Waste 71  
- Training of Staff Handling Waste Disposal in Operation Theatre 72
12. **Quality Control and Surveillance**  
*Nishat Hussain Ahmed, Gita Satpathy, Neelima Aron*
- Quality Control 73
- Microbiological Sampling 78
- Hospital Sterilization and Disinfection Policy 82

13. **Post-Cataract Surgery Endophthalmitis**  
*Anubha Rathi, Rohan Chawla, Atul Kumar*
- Microbial Spectrum of Post-operative Endophthalmitis 87
- *MRSA and MRSE*: Increasing Resistance to Topical Antibiotics 87
- Risk Factors and Incidence of Post-cataract Surgery Endophthalmitis 88
- Prophylaxis of Post-cataract Surgery Endophthalmitis 88
- Diagnosis and Management 90

14. **Post-Intravitreal Injection Infections**  
*Raghav Ravani, Rohan Chawla, Atul Kumar*
- Incidence and Risk Factors 94
- Clinical Presentation 94
- Diagnosis and Management 95
- Prophylaxis 96

15. **Endophthalmitis after Pars Plana Vitrectomy**  
*Karthikeya R, Rohan Chawla, Atul Kumar*
- Clinical Features 101
- Risk Factors 101
- Prophylaxis 102
- Management 103
- Outcomes 103

16. **Post-LASIK Infections**  
*Divya Singh, Neelima Aron, Prasida Goura, Namrata Sharma*
- Microbial Spectrum 105
- Risk Factors 105
- Clinical Diagnosis 106
- Prophylaxis 107
- Treatment: Medical and Surgical Therapy 108

17. **Infections after Intrastromal Corneal Ring Segments**  
*Deepali Singhal, Neelima Aron, Prasad Gupta, Rajesh Sinha*
- Risk Factors 110
- Etiological Organisms 110
- Pathogenesis 111
- Differential Diagnosis 111
- Clinical Features 111
- Microbiological Work-up 112
- Treatment 112
- Complications and Sequelae 112
- Prophylaxis 112
Ocular Infections: Prophylaxis and Management

18. Post-Collagen Cross-Linking Infections
   Jayanand Urkude, Neelima Aron, Anubha Rathi, Prafulla K Maharana, Namrata Sharma
   • Incidence 114
   • Risk Factors 114
   • Microbial Profile of Post-collagen Cross-linking Infection 115
   • Prophylaxis 115
   • Diagnosis and Management 116

19. Post-Keratoplasty Infections
   Neelima Aron, Prafulla K Maharana, Namrata Sharma
   • Risk Factors for Graft Infection and Prevention 119
   • Clinical Features 121
   • Investigations 123
   • Microbiological Spectrum 124
   • Management 124
   • Prevention 125
   • Outcomes 125

20. Bleb-Related Infections
   Neha Midha, Talvir Sidhu, Tanuj Dada
   • Incidence 128
   • Classification 128
   • Risk Factors 129
   • Microbial Spectrum 129
   • Prophylaxis 131
   • Diagnosis and Management 132
   • Visual Outcome and Prognosis 132
   • Patient Education and Counseling 133

21. Post-Strabismus Surgery Infections
   Saranya Devi K, Rohit Saxena
   • Incidence and Prevalence 136
   • Microbial Flora and Risk Factors 136
   • Endophthalmitis 137
   • Orbital and Preseptal Cellulitis 137
   • Scleritis 137
   • Surgically-induced Necrotizing Scleritis 138
   • Prophylaxis and Management 138

22. Post-Pterygium Surgery Infections
   Neelima Aron, Dhaya Agarwal, Prafulla K Maharana, Namrata Sharma
   • Incidence and Microbial Spectrum 143
   • Risk Factors 143
   • Pathogenesis 143
   • Clinical Presentation 144
   • Investigations 145
   • Management 145
   • Prophylaxis 147
23. **Infections after Ocular Surface Reconstruction Surgery** 149  
*Amreen Aslam, Renu Venugopal, Neelima Aron, Prafulla K Maharana, Namrata Sharma*

- Incidence 149  
- Risk Factors 150  
- Clinical Features 150  
- Investigations 151  
- Prophylaxis 152  
- Treatment 153  
- Coexisting Endophthalmitis 153

24. **Infections after Oculoplasty Surgery** 155  
*Amar Pujari, Rachna Meel, Neelam Pushker*

- Pre-operative Assessment 155  
- Intra-operative Precautions 155  
- Post-operative Care and Antibiotic Prophylaxis 156  
- Microbiology Profile 156  
- Antibiotics for Prophylaxis 156  
- Diagnosis and Management 157

*Index* 159
INTRODUCTION
In recent times, with the advent and use of anti-VEGF (vascular endothelial growth factor) agents for intraocular use, there has been a paradigm shift in the management of various medical retinal pathologies including neovascular age-related macular degeneration (AMD), diabetic retinopathy and macular edema and retinal vein occlusion. It is now known that VEGF plays a pivotal role in the pathogenesis of these conditions and intravitreal anti-VEGF agents are the first agents which have shown to improve visual acuity, rather than just prevent vision loss.

Endophthalmitis is one of the most dreaded complications of any intraocular procedure including intravitreal injections, causing severe ocular morbidity and vision loss.

INCIDENCE AND RISK FACTORS
The incidence of post-intravitreal injection endophthalmitis (PIE) is low. The incidence of post-cataract surgery endophthalmitis ranges between 0.09% and 0.33% in various studies, whereas that of suspected PIE has been reported to be around 0.038% and varies from 0.021 to 0.045%. Although the incidence is low, there is a worldwide dramatic increase in the number of injections performed annually, including India. Intravitreal injections is the most commonly performed medical procedure in the United States with numbers about twice as that of cataract surgery. Thus, PIE is a matter of grave concern, especially with confirmed reports of series of cluster endophthalmitis from our country following intravitreal injections. Cluster endophthalmitis has been defined as 5 or more cases occurring on a single surgical day and the same operating room at the center involved. Various risk factors predispose to the occurrence of PIE, including the condition for which the injection is given. The risk of infection seems to be lower in eyes with macular edema secondary to retinal vein occlusion as the indication of injection. The risk is more in patients with diabetic eye disease and neovascular AMD, with impaired or waning immunity as the hypothesized mechanism in both. Other risk factors (summarized in Table 14.1) include multiple patients undergoing the procedure in one sitting, improper storage of the drug or lapse in cold-chain (especially in drugs used as multidose vials, e.g. off-label use of bevacizumab), procurement of counterfeit drugs and multiple use of multi-dose vials, etc.

CLINICAL PRESENTATION
Clinical presentation, characteristics and suspected organisms causing infection in PIE is quite different from post-operative endophthalmitis (POE), with the former being more fulminant with a worse prognosis if not treated aggressively (Fig. 14.1).

Post-operative endophthalmitis may present as fulminant (<4 days), acute (5–7 days) or chronic form (>4 weeks). The time period of occurrence of PIE from injection to presentation is early and ranges from within 24 hours to even up to 26 days as reported, with an average of 4 days.
Table 14.1 Risk factors for post-intravitreal injection infections

<table>
<thead>
<tr>
<th>Associated with increased risk</th>
<th>Not associated with increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for injection (e.g. More risk in diabetes and AMD compared to vein occlusion)</td>
<td>Type of intravitreal anti-VEGF agent use</td>
</tr>
<tr>
<td>Improper storage/Lapse in cold chain</td>
<td>Hemisphere or quadrant of injection</td>
</tr>
<tr>
<td>Multiple use of multi-dose vials by repeated puncture of vials</td>
<td>Conjunctival displacement during procedure</td>
</tr>
<tr>
<td>Counterfeit drugs</td>
<td>Contaminated OT/irrigation fluids/failure of aseptic technique</td>
</tr>
<tr>
<td>Procedure performed in office-setting (risk if more when compared to operation theatre setting)</td>
<td></td>
</tr>
</tbody>
</table>

The most common symptom in both types of endophthalmitis is vision loss. The most frequent pathogens reported in PIE are gram positive bacteria (91.3%), especially coagulase-negative Staphylococcus (78.3%). Streptococcus viridans, a component of human oral flora has been reported to be present three times more often in PIE as compared to POE. Postintravitreal injection endophthalmitis needs to be differentiated from culture-negative sterile endophthalmitis, resembling toxic anterior segment syndrome (TASS) seen after intraocular surgery. A case series of such patients presenting with sterile endophthalmitis following intravitreal injection of bevacizumab has been reported from our center, highlighting the possibility of sterile endophthalmitis following intravitreal injection of bevacizumab.

**DIAGNOSIS AND MANAGEMENT**

Diagnosis of endophthalmitis following intravitreal injection is primarily clinical. As mentioned earlier, patients receiving intravitreal injection of bevacizumab may present with sterile endophthalmitis. In cases of doubt, it is important to consider all unexpected inflammatory response following injection or surgery to be endophthalmitis unless proven otherwise. The diagnosis can be confirmed by culture of causative organisms in vitro from intraocular samples. Samples that can be collected are aqueous tap or vitreous sample (higher yield) or both (preferred). A vitreous sample can be obtained by vitreous tap using 23-G needle through pars plana route before intravitreal antibiotic injections. However, due to the inadequacy of sample for analysis and theoretical risk of producing vitreous traction during aspiration, vitreous biopsy is preferred by many surgeons especially without infusion line to safely obtain adequate volume of sample that provides higher yield of organisms. This may be performed as a sole procedure or just before pars plana vitrectomy for endophthalmitis. The sample is then sent for staining for microscopic evaluation and culture and sensitivity.

Apart from confirmation of diagnosis in patients presenting with intraocular inflammation, it is also important to maintain and check records of the batch number of the drug used, and patients receiving injection on same day or injection from the same batch number. A drug vial from that particular batch number may also be sent for smear and culture which can help to trace the source of infection and early detection of other cases of endophthalmitis in the cluster if any.

Treatment in POE can be initiated following Endophthalmitis Vitrectomy Study (EVS) guidelines.
Ocular Infections: Prophylaxis and Management

This includes anti-bacterial therapy in the form of intravitreal antibiotics, anti-inflammatory therapy, supportive therapy or surgery. Concentrated topical antibiotics should be considered empirically till the culture results are awaited, especially if the route of infection spread seems to be from the anterior segment. Concentrated topical antibiotics may include cefazolin 5% and tobramycin 1.3%. Commonly used empirical intravitreal antibiotics include vancomycin 1 mg/0.1 mL and cefzazidime 2.25 mg/0.1 mL.

However, the treatment of PIE needs to be tailored depending upon individual cases. The treatment in PIE should be more aggressive as the infection tends to have a worse prognosis.

Though EVS concluded that there is no additional benefit of parenteral antibiotics in post-cataract surgery endophthalmitis, parenteral antibiotics help in augmenting and sustaining an adequate concentration of antibiotics in the vitreous cavity for a more prolonged period. Also, with the use of newer generations of antibiotics adequate MIC levels of the antimicrobial drugs in vitreous may be achieved when given parenterally, especially in cases of endophthalmitis, due to associated inflammation and resultant breakdown of the blood-retinal barrier. Thus parenteral antibiotics may be used, especially in post-intravitreal injection endophthalmitis which are usually fulminant and aggressive.

Like post-cataract surgery endophthalmitis, intravitreal antibiotics is the most common first line treatment in post-intravitreal injection endophthalmitis, however vitrectomy may be required for persistent vitritis, especially with atypical organisms. Early surgical intervention may be preferred in fulminant PIE. With the advancement in surgical techniques and equipment, the aim of surgery is to achieve complete vitrectomy with PVD induction, thereby removing the nidus of infection and significantly decreasing toxic and inflammatory load.

Undiluted specimen should be sent for culture studies and antibiotics should be injected in the vitreous cavity at the end of the surgery thereby achieving increased intraocular antibiotic concentration. A prospective randomized controlled trial at our center for post-traumatic endophthalmitis compared outcomes in patients that underwent core vitrectomy alone, to patients that underwent complete vitrectomy with silicone oil endotamponade. The study showed that complete vitrectomy with primary silicone oil endotamponade improved anatomical and functional results in post-traumatic endophthalmitis. Apart from being used as an internal tamponade after vitrectomy, silicone oil has been suggested to possess antimicrobial activity and could be preferred in post-intravitreal injection endophthalmitis.

**PROPHYLAXIS**

**Pre-operative Patient Screening and Precautions**

- The need and choice of intravitreal injection should be tailored to the individual patient as required in the best clinical judgment of the attending/injecting physician.
- Patients with uncontrolled systemic conditions like uncontrolled diabetes should first be treated for it.
- All patients should be screened to ensure patency of the nasolacrimal duct by a negative regurgitation test.
- Patients with active infection of the ocular adnexa (blepharitis, meibomitis), or a blocked nasolacrimal duct/positive regurgitation test are at high risk for endophthalmitis and should be treated for the active infection first. Injection should be postponed until the active infection is cleared.
- Surgical/Procedural time-out to verify patient’s name, intravitreal agent and laterality should be practiced before injection in each patient.
- Bilateral injections are not recommended and injection in the other eye should be spaced at least one to two weeks apart.
Drug Procurement or Preparation—
Precautions for use of Drugs
with Multi-Dose Vials

- Drug should be purchased from recognized dealers with proper receipt.
- Cold chain is to be maintained at each stage with proper temperature log maintenance.
- Note the batch number of each vial before opening.

Options for multiple injections from one vial (especially bevacizumab)

- **Ideally:** Compounding pharmacy to provide single dose ampoules. This constitutes dispensing of drug from vial (100 mg/4 mL) to sterile ampoules containing 0.2 mL for single use of 0.05 mL injection. This includes various tests including test of drug formulation for counterfeits (before dispensing), quality control tests and dispensing in sterile dispensing Good Manufacturing Practice (GMP) facility (class 10000 and class 10,000 environment) under laminar flow hood as is done at our center (Figs 14.3 and 14.4).

- Prepare multiple syringes by single puncture of vial under laminar hood. Store the syringes in a sterile container. Send 2 such syringes for culture. If culture negative, use the syringes for injection. The stored syringes are to be discarded after 2 weeks as there is minimal degradation of anti-VEGF activity of bevacizumab over first 2–3 weeks.16

- In case the facility for above two is not available (least preferred):
  - Pool up to 7 patients on the day of injection (the number has been empirically decided keeping in mind the financial viability of the procedure on one hand and prevention of loss of vision in many eyes in case of a cluster endophthalmitis)
  - Prepare 7 aliquots of around 0.2 mL per syringe (one syringe for one patient) inside the OT by single puncture of the vial after proper scrubbing and using aseptic technique
  - Re-cap the syringes with fresh sterile needles
  - Keep these syringes on a sterile surface
Ocular Infections: Prophylaxis and Management

- Only use these for the patients in the same session
- Discard the vial—It is not to be re-used or re-punctured

**Prophylactic Topical Antibiotics**

The studies on the role of topical antibiotics in the prevention of PIE concluded lack of evidence to support the administration of peri or post-injection topical antibiotics.\(^3\,17,18\) Thus pre-injection and post-injection topical antibiotics do not reduce the risk, in fact some studies showed a trend towards higher incidence.\(^3,18\) However, short course of post-procedure prophylactic antibiotics is used on surgeon’s personal experience and discretion.

**Patient Preparation**

- A written-informed consent should be taken from all patients, explaining the procedure and the risks involved. Off label use of bevacizumab is to be included in consent and explained to the patient.
- Each patient is to be given clean OT gown, protective cap and shoe-cover before entering the pre-operative holding area/operating room (Fig. 14.5).
- In the pre-operative holding area/or on table, the periorcular skin should be cleaned with povidone-iodine 10% solution.
- 10% povidone iodine should be used to clean the skin and ocular adnexa, 5% povidone iodine for instillation into the cul de sac with contact time of atleast 3 minutes (Figs 14.6A and B).
- Surgical area should be draped using sterile linen and a separate plastic eye-drape for each patient to isolate the field. A sterile speculum is placed to isolate the eyelashes away from the field (Figs 14.6C and D).

**Sterilization of Operating Room and Operating Room Milieu**

- **Location**: Intravitreal injection should be administered in the operating-room setting, and not in office-setting.
- **Sterilization and quality control**: should be done prior to intravitreal injections as discussed in detail in relevant chapters of the book.

**Intra-operative Precautions**

**Surgeon Factors**

- Surgeon should wear washed OT clothes, OT slippers, cap and mask.
- Surgeon should perform 3 scrubs with a solution equivalent to 2% w/v of chlorhexidine gluconate for at least 5-7 minutes under running water as per WHO recommendation. Details of scrubbing, gowning and gloving have been discussed in detail in the relevant chapters of the book.
- The surgeon/staff/patient should minimize speaking on table during preparation or during the injection procedure to minimize spread of aerosolized droplets containing oral contaminants.\(^6\)

**Peri-injection Precautions**

- Topical anesthetic drops should be preferred over anesthetic gel as the latter may interfere with povidone iodine contact with the conjunctiva/injection site.
- Reapply povidone-iodine after anesthetic drop use. Before injection, povidone-iodine (5%) should be the last agent applied to the intended injection site.
- Routine anterior chamber paracentesis is not recommended.

**Post-operative Precautions**

- Proper lid hygiene should be maintained in the post-operative period
- Post-injection topical antibiotics do not reduce the risk of infection/endophthalmitis.
Post-Intravitreal Injection Infections

- Post-injection IOP should be monitored and topical antiglaucoma drugs may be prescribed for post-injection IOP spike as and when warranted.
- All patients should be given a discharge card mentioning the injection details, post-operative instructions, symptoms of infection (pain, redness, dimness of vision, swelling, discharge etc.) and 24-hour emergency contact information.
- Follow-up of each patients should be tailored as per the indication for the intravitreal injections.
- Intravitreale injection of bevacizumab (Avastin®) for ophthalmic disorders may be considered at treating physician’s discretion, under strict aseptic precautions and following the recommended guidelines after informed consent of the patient. Intravitreal injection of medications for various posterior segment disorders has become one of the most common procedure performed worldwide. With extensive ongoing trials worldwide for various disorders involving intravitreal injection of different pharmacological agents, intravitreal injections have become a standard protocol and mainstay treatment for various pharmacological disorders. Endophthalmitis following intravitreal injection, though rare, is a dreaded complication causing significant ocular morbidity and vision loss. Following standard surgical procedures, precautions and maintaining asepsis can go a long way in preventing this complication and provide better outcomes.

Figures 14.6A to D Pre-operative cleaning (A and B), use of sterile plastic drape (C) and use of sterile speculum (D) to isolate the eyelashes away from the field before intravitreal injection
REFERENCES