

Review

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Review

Optimized Infection Control and Endophthalmitis Management in Ophthalmic Surgery: A Comprehensive Review of CEVE Strategy and Prophylaxis Protocols

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Abstract: The review summarizes the management of endophthalmitis – an inflammatory reaction in the eye, which may occur postoperatively, after injections or following open-globe injury. It may also occur as an endogenous process in immunologically compromised patients. Causative organisms **include** bacteria, fungi, or viruses, **some of which can be highly virulent**. It is an acute and urgent ocular pathology **with the potential for** imminent loss of sight and/or **the** eyeball. Sepsis may **also** be a real threat. **This is why** it is of utmost importance to introduce quick and **optimal** management, **with surgical treatment being the primary approach**. Complete and Early Vitrectomy for Endophthalmitis (CEVE protocol) seems to be the best solution. **The protocol for a One-Day Surgery Clinic set-up is described**. We summarise preventive measures for ocular surgeries and intravitreal injections. The use and dosing of antibiotics for endophthalmitis and **prophylaxis are** also discussed. One should be aware that **due to the increasing** microbial resistance **to** antibiotics, **their** overuse, subdosing, prolonged **usage**, or **unnecessary** treatment may deprive us **of an** effective **defense** against bacteria. In conclusion CEVE strategy is the most effective treatment for endophthalmitis, irrespective of the cause. Povidone iodine in perioperative management is the best solution for endophthalmitis prevention regardless of the cause. The use of antibiotics in the prevention of endophthalmitis should be **limited to a short yet sufficiently effective postoperative period** when prescribed in the form of drops. **However, it is strongly recommended following** eye surgery, especially after cataract extraction, **phacovitrectomy**, or MIGS procedures **involving** cataract removal. **Even though** it is still controversial, we recommend **against** routinely prescribing antibiotics **after** intravitreal injections **to prevent the promotion of bacterial resistance**.

Keywords: endophthalmitis; povidone-iodine; CEVE; CEVE algorithm; ocular surgery; antibiotics; prevention

1. Introduction

ENDOPHTHALMITIS is infection with a resulting inflammation of intraocular tissues and fluids with pus filling vitreal cavity and possible infiltration of inner coats of the eye wall. It may be postoperative, post-injection, post-traumatic or endogenous. (Kato et al. 2022; Soliman et al. 2019)

Bacteria are the most common cause, but fungi or viruses may also be responsible. It is an acute and urgent ocular pathology **that poses a risk of losing not only vision but also the entire eyeball**. If the pathogen **is highly virulent**, sepsis may **also pose a serious risk**.

Acute postoperative endophthalmitis **typically appears** 1-2 weeks following surgery, usually **within** 1-4 days. **This is why** it is of **utmost** importance to intervene **immediately** and **perform** complete surgery - Complete and Early Vitrectomy for Endophthalmitis (CEVE). **This protocol was introduced** in 2008, based on **the historical** indication „Ubi pus, ibi evacua.“ (Kuhn 2016; Morris & Kuhn 2021; Soliman et al. 2019)

Endophthalmitis requires immediate treatment. **From both** medical and legal **perspectives**, it should be initiated **without delay**, regardless of **the** chosen treatment. **Pathologically**, the presence of pus inside the eye **necessitates its** evacuation **as quickly as possible**, **primarily** because it can rapidly lead to irreversible vision loss (Kuhn 2016; Morris & Kuhn 2021; Soliman et al. 2019). **Therefore**, we believe **that** surgical treatment should be introduced immediately, **along with** antibiotics **such as** vancomycin, **first or second-generation** cephalosporins, **or fluoroquinolones**, **administered systemically**. (Pietras-Baczewska et al. 2021; Rejdak et al. 2016)

Complete and Early Vitrectomy is **essential** for retinal survival, especially **since** it is initially not known **which** organism **has caused** the endophthalmitis and **whether** a fulminant infection **will develop**. (Morris & Kuhn 2021)

Currently, the majority of ocular surgeries **are performed on** an outpatient **basis**, which **is why** we propose a protocol for **managing** endophthalmitis **in** one-day surgery centers, **as it ensures timely intervention**.

Endophthalmitis Management in Eye Surgery One-Day Clinic.

Endophthalmitis (**Figure 1**) is a rare but **severe** condition **that requires rapid and efficient action** to **preserve the patient's** vision, eye, and, **in cases of highly virulent pathogens**, even the patient's life.

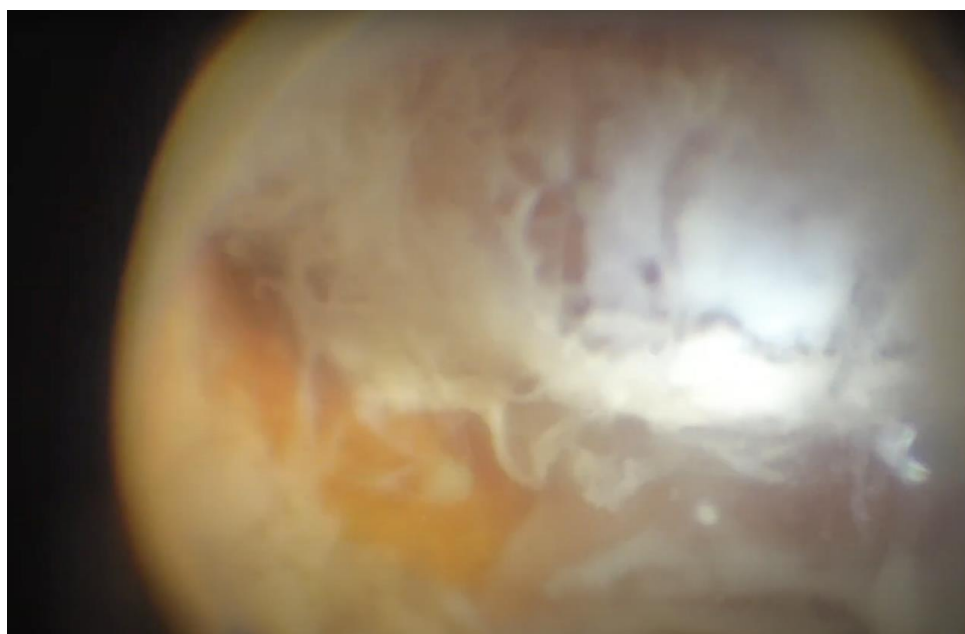


Figure 1. Acute postoperative acute endophthalmitis.

Every patient **experiencing** pain and/or vision deterioration **after** an operation or injection **who** **contacts the** registration office of **the** clinic should be examined as soon as possible, no later than **on the same day**. If the physician (CHANGE ALL IN THE MS) **detects symptoms or** suspects endophthalmitis, the patient should be **urgently** referred to a vitreoretinal (VR) surgeon. **It is advisable to have direct** contact with a VR surgeon **affiliated** with the clinic **or to arrange an immediate referral** to a hospital **equipped with a VR surgery unit**. **A sample for microbiological**

testing should be obtained either through a pars plana tap before referring the patient to a VR surgeon or at the beginning of vitrectomy. (Althiabi et al. 2022; Dave et al. 2022; Gower et al. 2017)

If the patient must travel a significant distance to the VR surgery unit, it is advisable to take a vitreous tap before referral and administer an intravitreal antibiotic injection (e.g., moxifloxacin, levofloxacin, or cephalosporin) via pars plana. This may help control the infection until a proper vitrectomy can be performed. We recommend implementing the Complete and Early Vitrectomy for Endophthalmitis (CEVE) strategy, which has been proven to be the most effective approach for endophthalmitis management. (Kuhn 2016; Morris & Kuhn 2021).

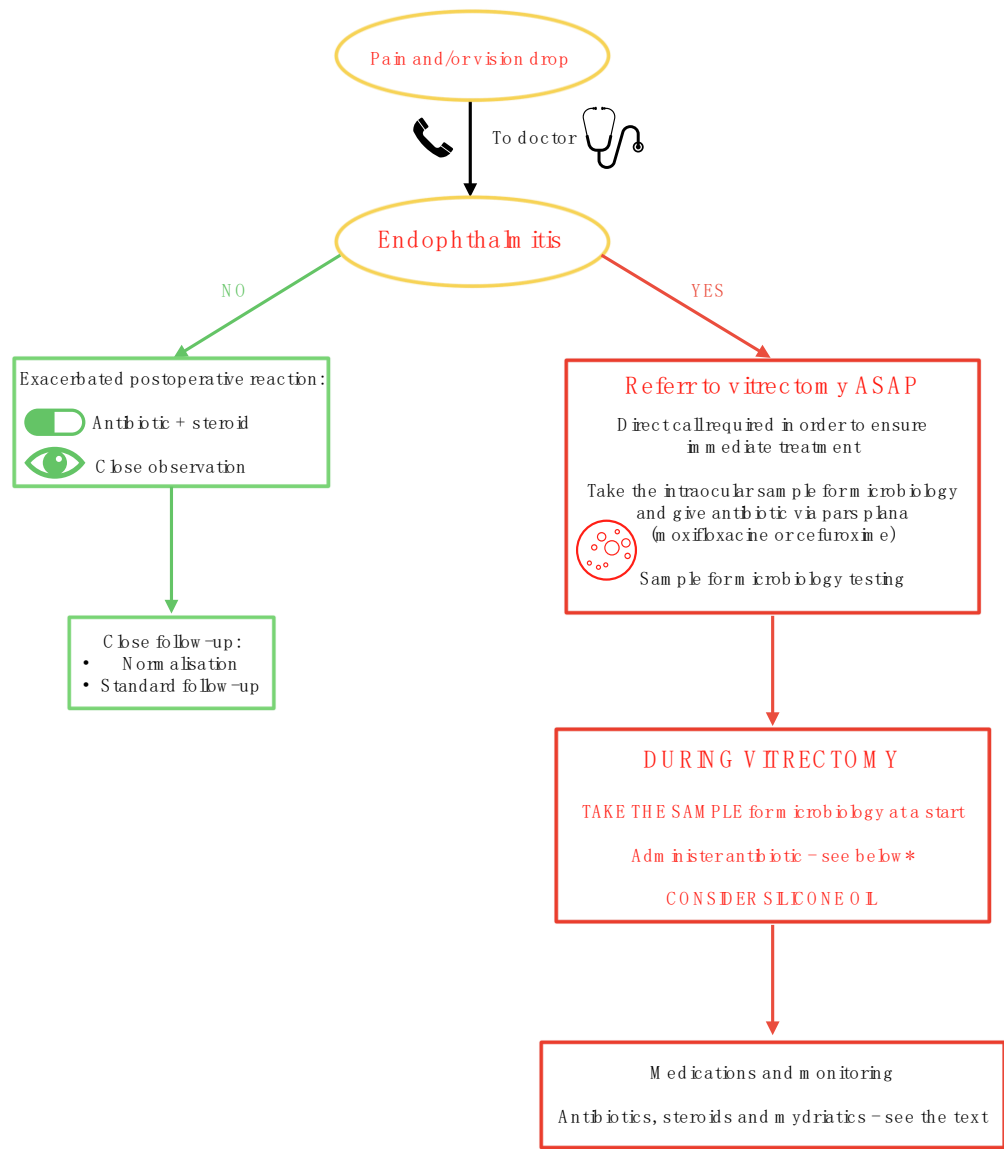


Figure 2. Endophthalmitis management in one-day clinic set-up.

Management should follow a decision-making tree as illustrated on Figure 3.

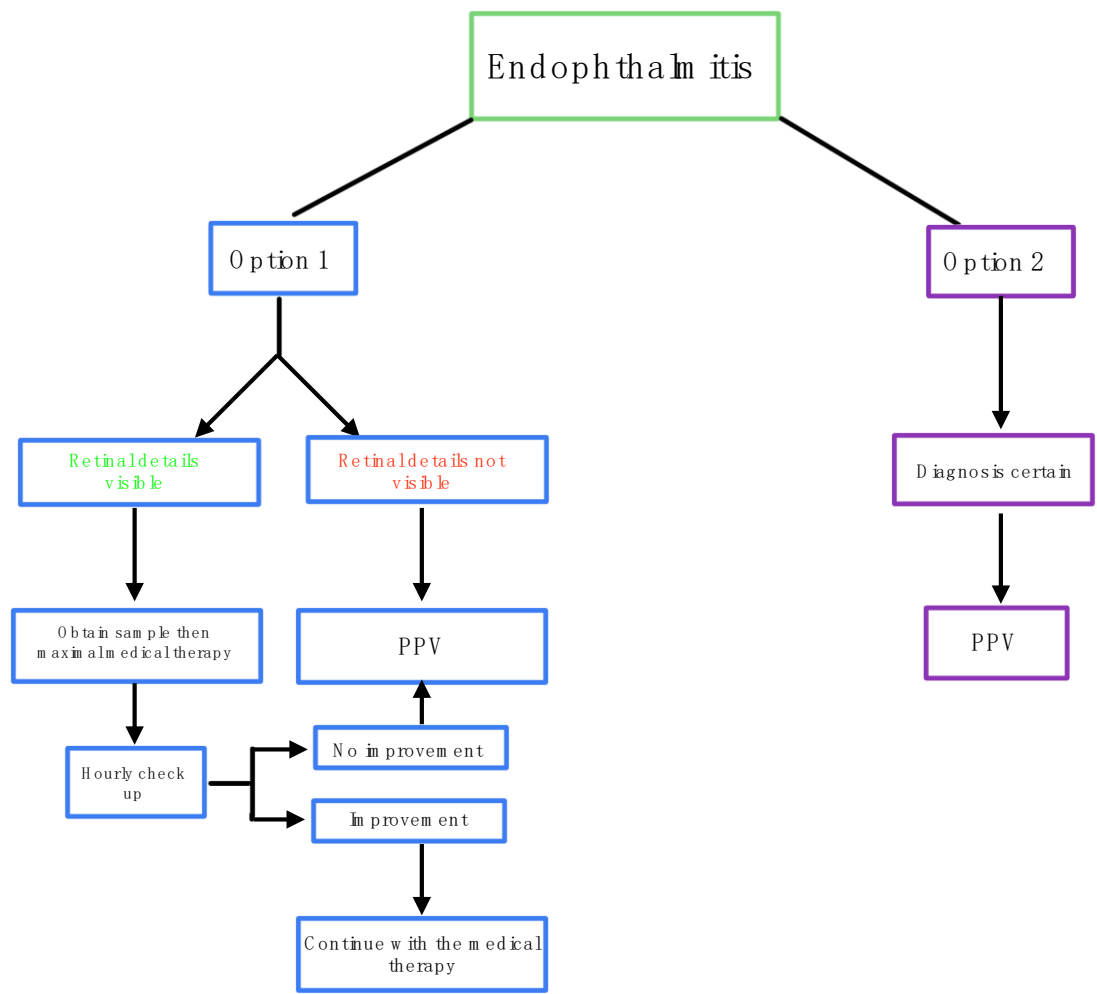


Figure 3. Decision making tree for endophthalmitis.

This algorithm focuses on the CEVE strategy and provides a straightforward guideline for eye surgeons: If there is any doubt, the condition should be treated as endophthalmitis, and vitrectomy should be performed as soon as possible. The presence of pus inside the eye requires its immediate evacuation and the use of all available treatment modalities against virulent pathogens. For this reason, pars plana vitrectomy is the default option. However, if the retina is visible, a sample may be taken via a vitreous tap, and the patient can be placed on maximum medical therapy with close follow-up. (Morris & Kuhn 2021)

Key Steps in Pars Plana Vitrectomy(Shao William B Yates I-Van Ho Andrew A Chang Matthew P Simunovic):

1. After trocar insertion, obtain samples from the vitreous cavity and the anterior chamber for microbiological testing.
2. During vitrectomy, administer a broad-spectrum antibiotic via infusion fluid (e.g., vancomycin 0.2 mg/ml in 500 ml Ringer’s solution) (Pietras-Baczewska et al. 2021; Rejdak et al. 2016)
3. Perform intraoperative anterior chamber lavage using a broad-spectrum antibiotic.
4. Remove pus, ensuring posterior vitreous detachment to clean the retinal surface as thoroughly as possible, and examine the ciliary body and vitreous base.
5. Address any pre-existing ocular pathologies, such as retinal detachment.
6. At the conclusion of the procedure, leave an appropriate antibiotic in the vitreous cavity (see Table 1 for dosages).

7. **Consider using a silicone oil tamponade**, as **silicone oil has bacteriostatic properties** and may help prevent late complications **such as retinal detachment or eyeball atrophy**.(Sinisi et al. 2022; Weber et al. 2023)

The CEVE protocol means a vitrectomy that is performed as soon as possible once the diagnosis has been made. “Early” aims for a stage when the damage to intraocular tissues is still minimal, and a vitrectomy where safety is not compromised by either poor visibility or necrotic retina.

The CEVE protocol also means a vitrectomy where pus is not left on the posterior retina (“macular hypopyon”), which means the still-attached posterior hyaloid is surgically detached, consistent with safety.

Conversely, despite this vitrectomy being termed “complete”, it is limited anteriorly, at the vitreous base, to reduce the risk of iatrogenic retinal injury, which would threaten with postoperative retinal detachment.

Table 1. Intravitreal antibiotics and their doses.(Brockhaus et al. 2019).

Antibiotic agent	dose
Moxifloxacin (Vigamox)	500ug/0,1 ml
Vancomycin	1mg/0,1 ml
Ceftazidime	2,2 mg/0,1 ml;
Cefuroxime (Aprokam)	1mg/0,1 ml
Amikacine (Amikin)	0,m4mg/01, ml
Amphotericinum B- anti-fungal agent	5ug/0,1ml

Postoperatively, **broad-spectrum antibiotics should be administered topically on an hourly basis**. **Topical steroids**, such as dexamethasone (every 2-3 hours), and **mydriatics** (e.g, atropine or tropicamide, 2-3 times daily) should also be used. Once the antibiogram results are available, **treatment should be adjusted accordingly**.

Patients should remain under close observation, with daily follow-up visits if necessary. Every **endophthalmitis case** should be reported to the **Infection Control Group** within the clinic or hospital (**if applicable**) and documented in the Electronic Adverse Events Registry. **An example of such a registry is depicted in Figure 4.**

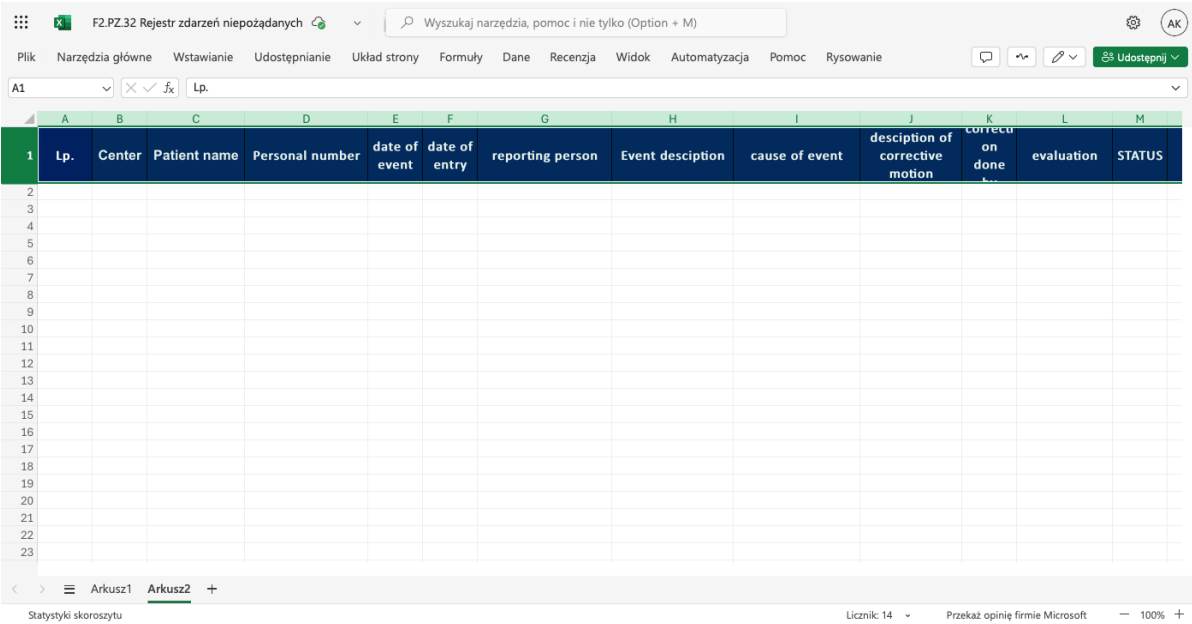


Figure 4. Adverse Events Registry.

2. Prevent Before It Happens

Endophthalmitis prophylaxis **during ophthalmic surgical procedures, such as** cataract extraction, vitreoretinal (VR) surgery, or any other surgery, should **include** preoperative, intraoperative, and postoperative management. **Preoperatively**, eyelid margin evaluation should be performed **to assess for** conditions such as rosacea, excessive biofilm on eyelashes or eyelid margins, and exacerbated dry eye. **These conditions must be treated before surgery** to maintain **ocular surface balance** and ensure a **safer** surgical outcome. **Many infections arise from the patient's own flora, introduced from the ocular surface into the eye during surgery.** Staphylococcus epidermidis and **even** Staphylococcus aureus are part of the **natural** ocular surface flora (Kudasiewicz-Kardaszewska et al. 2023b). However, **when introduced into** the vitreous cavity, **these bacteria may become** virulent and **cause** severe infections.

While **complete** sterilization of the ocular surface is impossible, it is **essential** to restore **its** balance before surgery and disinfect it properly **before the procedure** (Grzybowski & Brona 2017).

2.1. Preoperative Measures

For **patients with chronic blepharitis**, standard **treatment** should include eyelid thermotherapy, hygiene with special wipes, and artificial tears **as a minimum requirement** (Kudasiewicz-Kardaszewska et al. 2023b).

Additionally, **in cases of severe blepharitis, applying mupirocin ointment** to the nose and/or face (e.g., Mupine, Mupirox) **may be considered** to **reduce** Staphylococcus populations on the eyelids and facial skin. **This is particularly important for minimizing methicillin-resistant Staphylococcus aureus (MRSA) strains.** The ointment should be applied **to the nostrils** 2-3 times daily for five days before surgery (Trautmann et al. 2007).

2.2. Prevention in the Operating Room (OR)

All personnel **present** in the **operating room** should wear **proper OR attire, including** gowns, caps, and boots **specifically designated** for the OR environment. Face masks should cover both the **mouth and nose, particularly** **over the sterile operating field.** If a mask becomes moist, contaminated, or comes into contact with bodily fluids, it must be replaced immediately.

The laminar airflow system and/or air conditioning should be **operational at least one hour before surgery begins** and remain **active** throughout all procedures. **Turning off the laminar flow system due to personal discomfort (e.g., feeling cold air on the neck) is discouraged.** Instead, surgeons may wear an **additional layer underneath their sterile gown** for comfort.

The **surgeon must carefully scrub** their hands using **sterile soap and warm water, paying special attention** to nail hygiene. Nails should be short and free of polish or debris. Special sterile spatulas can be used to clean under the nails. Hand washing should last **at least 40-60 seconds** (Farhoudi et al. 2016). The **sequence of hand washing and disinfection** is shown in Figure 5.



Figure 5. Hand washing (A) and disinfection (B) sequence according to WHO. (Pittet 2009).

According to WHO (2008), if antimicrobial soap and **clean** water are **available**, additional disinfection is **not necessary**. However, in **practical** settings, **surgeons should perform surgical handwashing to remove any visible contaminants** before entering the OR. **Subsequently, a disinfectant should be applied to the hands and forearms for at least 1-3 minutes (up to 5 minutes if necessary)**. Disinfection **targets** the surgeon’s and nurses’ **own flora** and should be **repeated between surgeries**. Hand washing **should also be performed** after using the restroom, eating, coming into contact with blood or body fluids, or returning to the OR **from another area**. (Pittet 2009).

After **hand scrubbing and disinfection**, the surgical team (**including the surgeon and scrub nurse**) should wear a **sterile gown and gloves**. The **scrub nurse should prepare a table with sterilized and disposable sterile equipment**. Either the **scrub nurse or the surgeon** should disinfect the **operative field**. For eye surgery, this involves applying **7.5% or 10% povidone-iodine** to the **eyelids, orbital area, forehead, and cheek** (twice for 30 seconds each time) and **5% povidone-iodine to the ocular surface before surgery and after speculum insertion** (Grzybowski & Brona 2017). Povidone-iodine has been proven to be the **most effective antiseptic for preventing postoperative endophthalmitis**.(Grzybowski et al. 2022).

Povidone-iodine is a **broad-spectrum antimicrobial agent that works by destroying microbial DNA and proteins**(Singh et al. 2021). It is effective against **bacteria, viruses, chlamydia, and fungi**. Evidence-based data **show** that povidone-iodine reduces the **bacterial population on the ocular surface (both cornea and conjunctiva) by a factor of 100**.(Ciulla et al. 2002)



Figure 6. Skin and ocular surface ready for operation: Skin disinfected with 10% povidone-iodine, ocular surface with 5% povidone-iodine, sterile drape applied, eyelids held open with a speculum, eyelashes separated from the surgical field using a surgical foil.

2.3. Controversies Regarding Preoperative Topical Antibiotics

There is ongoing debate regarding the use of **topical antibiotics** (e.g., levofloxacin or tobramycin) before surgery. **Based on our experience, it may be beneficial, especially for patients with stage III or IV blepharitis** (even in remission) or **monocular** patients. However, antibiotics should be **instilled at least 30 minutes before surgery**. Some **surgeons advocate for administering antibiotic prophylaxis 3-5 days preoperatively**; however, **this should be based on microbiological analysis to avoid unnecessary antibiotic use and reduce the risk of bacterial resistance**.

2.4. Proper Draping and Ocular Surface Preparation

After applying povidone-iodine, a sterile drape with plastic foil should be placed over the surgical field. **The first application of 5% povidone-iodine drops should be instilled onto the ocular surface before draping. A second application (2 ml) should be performed after the drape and speculum are in place as a lavage over the entire ocular surface. If irrigation with normal saline or Ringer's solution is performed, povidone-iodine should remain in contact with the ocular surface for at least three minutes to be effective**(Borgia et al. 2023).

Table 2. Preparation of 5% Povidone-Iodine Solution:.

Initial Povidone-Iodine Concentration	Dilution Ratio	Preparation Method (10 ml syringe)
10% Povidone-Iodine	1:1	5 ml of 10% PI + 5 ml Ringer’s solution or BSS
7.5% Povidone-Iodine	2:1	6 ml of 7.5% PI + 3 ml Ringer’s solution or BSS

By following these standardized antiseptic and hygiene protocols, the risk of postoperative endophthalmitis can be significantly reduced.

If a monocular patient wears a prosthesis, it must be removed 3-5 days preoperatively and the conjunctival sac sterilized for 3-5 days using povidone-iodine 10%.

2.4.1. Intraoperative Endophthalmitis Prophylaxis

The use of intracameral antibiotics, such as cefuroxime (Aprokam, 0.1 mg/0.1 ml) or moxifloxacin (off-label in Europe but approved in India as Auromox 0.5%), is essential for reducing the risk of postoperative endophthalmitis. Studies have demonstrated that intracameral cefuroxime reduces the endophthalmitis rate from 0.59% to 0.039%, while moxifloxacin decreases the risk fourfold among cataract patients(Rękas et al. 2020). Research conducted outside Europe has also shown that intracameral moxifloxacin significantly lowers postoperative infection rates while ensuring safety.(Arshinoff & Modabber 2016; HariPriya et al. 2016; Leung et al. 2018).

Moxifloxacin is also used in the vitreous cavity at the conclusion of cataract surgery in so-called ‘dropless cataract surgery.’ Special formulations, such as Tri-Moxi (triamcinolone and moxifloxacin), have been administered via pars plana or transzonular routes to eliminate the need for postoperative antibiotic-steroid drops(Assil et al. 2021). However, Tri-Moxi-Vanc (triamcinolone, moxifloxacin, and vancomycin) has been associated with an increased incidence of hemorrhagic occlusive vasculitis, and its use is therefore discouraged. (American Society of Cataract and Refractive Surgery. Clinical alert: HORV association with intraocular vancomycin. Ascrs.org/clinical-education/clinical-reports/2016-cr-clinical-alert-horv-association-with-intraocular-vancomycin . Last accessed June 3, 2020. 2020)

The application of 5% povidone-iodine at the end of surgery, before any other drops or ointments, is another crucial antiseptic step in infection prevention(Grzybowski et al. 2022).

2.4.2. Postoperative Management

It is recommended to prescribe a high-concentration antibiotic for a short duration. In practice, a combination antibiotic-steroid drop should be used four to five times daily for seven days, followed by a steroid-only drop for an additional seven days. Non-steroidal anti-inflammatory drugs (NSAIDs) are advisable twice to four times daily for 2-4 weeks postoperatively. There is no need for gradual steroid tapering. The proposed postoperative treatment regimens are detailed in Table 3.

Table 3. Proposed Postoperative and Anti-Inflammatory Medication Regimens Following Cataract Surgery and Combined Procedures Involving Cataract Extraction with PPV or MIGS.

Medication	Duration	Frequency of application
Broad-spectrum antibiotic*	5-7 days	4-5 times a day
Steroid**	2-3 weeks	4 times a day
NSAID	4 weeks if applicable	2-4 times a day

*fluoroquinolones (levofloxacin or ofloxacin) or aminoglycoside (tobramycin or gentamycin); **May be a combination medication containing both an antibiotic and steroid (e.g., Duressa, Maxitrol, Tobradex, or Dexamyltrex).

2.4.3. Special Considerations for Intravitreal Injections

Millions of intravitreal injections are administered worldwide daily for macular and retinal diseases. While the procedure is simple, a lack of caution can lead to devastating complications, such

as isolated or clustered cases of endophthalmitis (e.g., 2-6 cases in a row). (Einan-Lifshitz et al. 2021; Pietras-Baczewska et al. 2021).

It is recommended that intravitreal injections be performed **either in the OR or in a dedicated treatment room**. All staff should wear **appropriate attire, including OR gowns, boots, caps, and surgical masks covering the nose and mouth**. **Strict adherence to face mask policies is crucial, as studies have demonstrated that properly worn masks are more effective in preventing oral flora-associated infections than a 'no talking' policy**(Patel et al. 2021). The scrub nurse should prepare medications for injections in sterile manner(Grzybowski et al. 2018).

Patients **should also be encouraged to practice home eyelid hygiene** using sterile ocular wipes particularly in monocular patients or those receiving multiple injections over extended periods.(Baudin et al. 2022)

2.4.4. Povidone-Iodine Use in Intravitreal Injections

The following povidone-iodine concentrations should be used before intravitreal injections (Einan-Lifshitz et al. 2021; Reibaldi et al. 2019; Safar & Dellimore 2007):

- **7.5-10% for skin disinfection before draping and speculum insertion (applied twice).**
- **5% for ocular surface disinfection before skin preparation, after draping, immediately before injection, and again post-injection before removing the drape.**

Povidone-iodine should be free from soap components such as glycerol to avoid disruption of the mucin layer in the tear film. **Since patients often return regularly for injections, protecting the ocular surface is crucial.** The use of an **operating microscope or magnifying lamp for injections is recommended** to improve precision and visualization(Teberik et al. 2019).

2.4.5. Managing Patients with Povidone-Iodine Sensitivity

A true allergy to povidone-iodine (i.e., a Type I hypersensitivity reaction) is **rare** (Hinkle et al.; Nair et al. 2023) **Most adverse reactions involve mild irritation, such as itching, excessive tearing, or conjunctival redness.** If a patient has a history of iodine allergy, povidone-iodine **can still be used at its standard concentration but should be rinsed out with balanced salt solution (BSS) immediately afterward. The patient should remain under observation for 30-60 minutes post-procedure.** If excessive itching, swelling, or redness occurs, systemic antihistamines (e.g., cetirizine or bilastine) and mild topical steroids **can be prescribed for 5-7 days.**

If povidone-iodine **must be avoided**, chlorhexidine **can be used instead for skin and ocular surface disinfection.**(Kancierz & Myers 2022)

2.4.6. Antibiotics Following Intravitreal Injections: To Prescribe or Not?

Evidence-based medicine (EBM) **does not support routine antibiotic prescription** after anti-VEGF injections. **Studies have shown that topical antibiotics do not reduce the rate of endophthalmitis but do contribute to bacterial resistance**(Baudin et al. 2022; Morioka et al. 2020).

Doctors may consider antiseptic drops (e.g., containing chlorhexidine or polyhexanide) **for high-risk patients, such as monocular or immunocompromised individuals, or those with severe ocular surface disease**(Kancierz & Myers 2021).

An exception to these recommendations is dexamethasone implant injection, where broad-spectrum antibiotics should be prescribed **for 5-7 days post-injection**. This is due to the **larger (19 g) needle used for drug delivery, increasing the risk of bacterial contamination.** However, since dexamethasone implants are administered **only every 4-6 months, rather than as frequently as anti-VEGF agents**, antibiotic prophylaxis remains justified. (https://ec.europa.eu/health/documents/community-register/2017/20171115139165/anx_139165_pl.pdf)

By implementing these **comprehensive intraoperative and postoperative protocols**, the incidence of endophthalmitis can be **substantially reduced**, improving patient safety and surgical outcomes.

3. Conclusions

The **Complete and Early Vitrectomy for Endophthalmitis (CEVE) strategy is the most effective treatment for endophthalmitis, regardless of its underlying cause.**

Perioperative povidone-iodine application remains the most effective measure for preventing endophthalmitis in ocular surgery. The broad-spectrum antimicrobial properties of povidone-iodine help **significantly reduce bacterial load**, lowering the risk of postoperative infection.

The use of antibiotics for endophthalmitis prevention should be limited to a high concentration for a short duration when administered as eye drops. However, **intracameral antibiotics are strongly recommended at the conclusion of eye surgery, particularly following cataract extraction, phaco-vitrectomy, or MIGS procedures involving cataract removal.**

Despite ongoing controversy, we strongly recommend against the routine use of prophylactic antibiotics following intravitreal injections, as they do not reduce the risk of endophthalmitis but contribute to bacterial resistance. Instead, **proper antiseptic measures, including povidone-iodine application, remain the most reliable approach to infection prevention.**

By adhering to **comprehensive infection control measures, including rapid surgical intervention, optimized prophylactic regimens, and strict perioperative protocols**, ophthalmic surgeons can **substantially reduce the risk of endophthalmitis and improve patient outcomes.**

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