Chapter 14
Endophthalmitis After Intravitreal Injections

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Intravitreal injection is the most commonly performed procedure by retina specialists. As per reports in the USA, the number of injections performed has increased from 82,994 in 2004 to 2.5 million injections in 2011 [1].

Anti-vascular endothelial growth factor (VEGF) injections are the standard of care in neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and macular edema due to retinal vein occlusion (RVO). The commonly used agents are ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA), bevacizumab (Avastin; Genentech Inc., South San Francisco, CA), and aflibercept (Eylea; Regeneron Inc., Tarrytown, NY). The most serious vision-threatening adverse event after intravitreal injection is endophthalmitis. Bacteria can enter immediately into the vitreous cavity at the time of injection [2, 3]. Bacterial sources include the patient's ocular or periocular surfaces, aerosolized bacteria, or contamination of the needle, instruments, drug, or drug vial [4]. The rate of endophthalmitis after intravitreal injection is low, with reports in the literature ranging from 0.01% to 0.08% [5–7]. A recent meta-analysis of 43 published articles reported an overall incidence of endophthalmitis following anti-VEGF injection at 0.056% [8]. The most commonly isolated organisms were coagulase-negative *Staphylococcus* (Fig. 14.1) and *Streptococcus* species.

In spite of the extensive use of injections, evidence on relative safety with regards to endophthalmitis risk is limited. Rayess et al. studied 183 cases of endophthalmitis from approximately 500,000 anti-VEGF injections (overall rate of 0.036%) [9]. The rates of endophthalmitis were 0.039% in bevacizumab group, 0.035% in ranibizumab group, and 0.035% in aflibercept group (Table 14.1). These differences were not significant. Coagulase-negative *Staphylococcus* and *Streptococcus* species were the commonly isolated organisms in all three groups (Table 14.1). Overall, visual outcomes were better in culture-negative than culture-positive cases at 3 months

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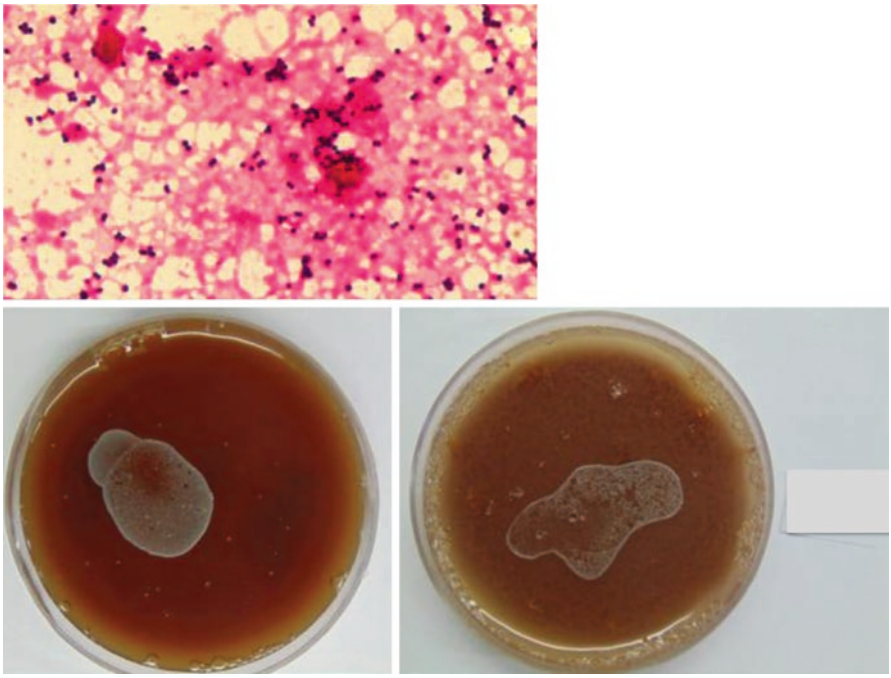

Fig. 14.1 *S. epidermidis* growth in a patient after intravitreal injection of Avastin. (*Top*) Gram stain at 100× magnification showing gram-positive cocci in groups; (*bottom*) blood (*left*) and chocolate (*right*) agar showing moist colonies without hemolysis (courtesy: Joveeta Joseph, Ph.D.)

Table 14.1 Occurrence of endophthalmitis with bevacizumab, ranibizumab, and aflibercept [9]

Molecule	Total injections	Endophthalmitis n	Rate	Common organisms
Bevacizumab	153,812	60	0.039%	*Staphylococcus* (69.6%) *Streptococcus* (21.7%)
Ranibizumab	309,722	109	0.035%	*Staphylococcus* (43.9%) *Streptococcus* (22%)
Aflibercept	40,356	14	0.035%	*Staphylococcus* (50%) *Streptococcus* (50%)

follow-up. Furthermore, culture-positive cases due to coagulase-negative *Staphylococcus* had better visual outcomes at 3 months than those related to *Streptococcus* species for all groups.

Endophthalmitis was reported after a mean of approximately 4 days from the day of injection. Mean logMAR visual acuity was 0.74 ± 0.54 (Snellen equivalent: 20/110) before the injection (baseline) and decreased to logMAR 2.27 ± 0.86 (Snellen equivalent: counting fingers, $P < 0.001$) at diagnosis of endophthalmitis. At 3 months follow-up, the visual acuity improved to logMAR 1.14 ± 1.04 (Snellen

Table 14.2 Comparison of endophthalmitis rates after anti-VEGF injection and intravitreal steroid injection [11]

Molecule	Total injections	Endophthalmitis	Rate
Anti-VEGF	387,714	73	0.019%
Steroid	18,666	24	0.13%

equivalent: 20/276, $P = 0.005$ compared to baseline vision). Although the average visual acuity improved after treatment for endophthalmitis, it was worse than the mean pre-injection visual acuity. Similar results have been shown by a study from the Bascom Palmer Eye Institute at Florida, USA [10].

The risk of endophthalmitis after an intravitreal steroid injection is much higher compared with an anti-VEGF agent injection [11]. A total of 75,249 beneficiaries in a large national US medical claims database representing 406, 380 intravitreal injections were studied. Approximately 400,000 anti-VEGF injections and 19,000 steroid injections were performed. There were 73 cases of endophthalmitis following intravitreal anti-VEGF injections (rate = 0.019% or 1 in 5283 anti-VEGF injections) and 24 cases of endophthalmitis after corticosteroid injections (rate = 0.13% or 1 in 778 steroid injections). After controlling for diagnosis, age, race, and gender, the odds ratio (OR) for occurrence of endophthalmitis was 6.92 (95% confidence interval, 3.54–13.52, $P < 0.001$) times higher post-corticosteroid injection compared with anti-VEGF injections [11] (Table 14.2).

There is a debate on whether the distribution of bevacizumab through compounding pharmacies increases the risk for endophthalmitis compared to the distribution of single-use vials of ranibizumab from the manufacturer. Vander Beek et al. reported their 8-year results (January 2005–December 2012) of intravitreal injections [12]. This analysis included 296,565 bevacizumab injections to 51,116 patients and 87,245 ranibizumab injections to 7496 patients. There were 71 cases of endophthalmitis (49 in the bevacizumab cohort and 22 in the ranibizumab cohort) for an endophthalmitis rate of 0.017% for bevacizumab and 0.025% for ranibizumab. There was no significant association with development of endophthalmitis after a bevacizumab injection compared with ranibizumab (odds ratio, 0.66 [95% CI, 0.39–1.09]; $P = 0.11$) [12].

Preoperative Prophylaxis

There are currently no randomized clinical trials evaluating the role of prophylactic topical antibiotics in this setting. Many large series have reported that topical antibiotics do not decrease the rate of endophthalmitis. This may be related to changes in the conjunctival flora due to repeated exposure to antibiotics. At this time, povidone-iodine, rather than antibiotics, is preferred for the majority of patients undergoing intravitreal injections [13].

Location of Operating Room vs. Outpatient Clinic

In the 2013 American Society of Retinal Specialists (ASRS) Preferences and Trends (PAT) Survey, over 98% of USA-based specialists reported performing injections in an office setting, compared with only 47% of international specialists [14]. In Germany and other parts of Europe, more number of injections were performed in the operating room (OR) [15]. The endophthalmitis rate has been reported to be 0.12% for office-based injections compared to 0% for OR-based injections [16].

Gloves

Even though no study has been done to analyze the role of gloves, complete aseptic precautions should be taken during intravitreal injections, as is the standard for any other intraocular surgical procedure. Since the vitreous is an avascular protein-rich tissue, even minimal bacterial contamination could lead to serious infection.

Face Mask

Surgical facemask is essential to eliminate any accidental bacterial contamination of the eye from the surgeon's mouth or nasopharynx [17]. Facemask should be even worn by those assisting in the injection procedure. As per the 2013 ASRS PAT survey, 14% of ophthalmologists reported wearing a mask during intravitreal injections [14]. In a meta-analysis of over 100,000 injections, McCannel found that almost a third of the cases were due to *Streptococcus* species. This was threefold higher than earlier studies of endophthalmitis after cataract surgery [18]. *Streptococcus* contamination is associated with poor visual acuity and an increased likelihood of enucleation. *Streptococcus viridans* are normal commensals of the upper respiratory tract and oral cavity [18, 19]. Since they are uncommonly found as part of the normal conjunctival flora, the contamination could occur from aerosolization [7, 18].

A mask may also offer protection in the event of an inadvertent cough or sneeze. The needle should remain capped until immediately before the injection [5]. Patients should be instructed to minimize talking before or during the procedure.

Povidone-Iodine

Povidone-iodine is a complex of iodide and polyvinylpyrrolidone (PVP), which acts as a reservoir of "free" iodine, and is the active component [20, 21]. The iodine penetrates cell membranes and inactivates intracellular proteins, fatty acids, and

nucleotides. It has broad-spectrum antimicrobial activity with negligible bacterial resistance. A recent survey found that over 99% of retinal specialists use povidone-iodine before intraocular injections [22].

In a randomized study, 5% povidone-iodine instilled into the conjunctival sac prior to ophthalmic surgery reduced the number of bacterial colonies by 91%, compared to a 33% reduction in control eyes [23]. In an open-label nonrandomized trial, Speaker and Menikoff found that the incidence of culture-positive endophthalmitis was 0.06% using 5% povidone-iodine, compared to 0.24% using silver protein solution [24]. In contrast, using a 2-min contact time, Ferguson et al. [25] found that 5% povidone-iodine was more effective than 1% povidone-iodine at reducing the number of colony-forming units, particularly in the presence of a heavier initial bacterial load.

Antibiotics

In the ASRS PAT Surveys, the percentage of respondents using pre-injection topical antibiotics has reduced from 40% in 2008 to 27% in 2011. The percentage using postinjection topical antibiotic has also reduced from 86% in 2008 to 62% in 2011. In 2013, 78% of US respondents indicated no use of pre- or postinjection topical antibiotics.

Pre-injection Antibiotics

No studies have shown any substantial benefit of pre-injection topical antibiotics to reduce the risk of endophthalmitis. Using antibiotics just 1–2 h preoperatively conferred no additional benefit over povidone-iodine alone in two studies [26, 27].

Antibiotics have been used post injection in several series without affecting the endophthalmitis rate [28–30]. In fact, a nonstatistically significant higher rate of endophthalmitis has been found in patients receiving postinjection antibiotics in a number of studies [31–34]. Coagulase-negative *Staphylococcus* endophthalmitis isolates resistant to fluoroquinolones at Bascom Palmer Eye Institute increased from 0% to 60.5% in 1990–2011 [34–36]. It is suspected that the widespread use of fluoroquinolones is responsible for the increasing resistance.

The LVPEI Experience [30]

We reported endophthalmitis in 8 of 15,925 anti-VEGF injections (0.05%), and this included four cases occurring in a cluster infection. All injections were given in minor theater exclusively for intravitreal injections. Seven of eight vitreous biopsies

grew coagulase-negative *Staphylococci* (CONS); this included four cluster cases growing *Staphylococcus hominis*, and one vitreous biopsy grew *Staphylococcus sanguinis*. Following vitrectomy and intravitreal antibiotic injection, four of eight patients recovered to 20/200 visual acuity at least. Repeat vitrectomy and intravitreal antibiotics were required in five patients.

It is critically important to avoid contaminating the needle with the eyelashes or lid margins before or during entry into the globe, as direct inoculation is considered to be the major mechanism by which endophthalmitis occurs [37].

A closed-blade speculum is superior to an open-blade speculum as it covers the eyelashes more effectively. In the VISION study, the most common reason for endophthalmitis was the failure to use an eyelid speculum [37]. It has been recommended that povidone-iodine should be instilled again after speculum insertion.

Conclusion

Intravitreal injection is already a standard of care in variety of retinal diseases. It is also a fact that in more common causes, such as in AMD, diabetic retinopathy, and other retinal vascular conditions, more than one injection is needed and has to be given for a longer duration of time, sometimes up to 1 year. Additionally, these injections are given to patients who are either old (AMD) or otherwise compromised due to diabetes mellitus and hypertension. Hence it is imperative that enough care is taken to prevent infection. In addition to maintaining absolute sterility during the process, there is conclusive evidence only for perioperative use of povidone-iodine and not for topical antibiotic either before or after the intravitreal injection.

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